Contents

Multiple Micronutrient Supplementation During Pregnancy in Developing Country Settings

Guest editors: Nita Dalmiya, Ian Darnton-Hill, Werner Schultink, and Roger Shrimpton

Note From the Editor

The publication of this supplement of the *Food and Nutrition Bulletin* is noteworthy in that it marks the culmination of a decade of collaboration and research.

Policy making for global application is challenging and increasingly demanding of a solid base of evidence, if not consensus. The process presented in this supplement to the *Food and Nutrition Bulletin* sets a high standard.

The leadership of SCN, UNICEF, the funding of supporting agencies, and the diligence of the participants is exemplary, and will lead to the strongest policy.

Irwin H. Rosenberg
Editor-in-Chief

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Multiple micronutrient supplementation during pregnancy: a decade of collaboration in action

Nita Dalmiya, Ian Darnton-Hill, Werner Schultink, and Roger Shrimpton

The starting point for this collaboration was recognition that deficiencies of vitamins and minerals beyond iron deficiency are widely prevalent among women of reproductive age, particularly pregnant and lactating women in developing countries, and that some of these deficiencies have a negative impact on pregnancy outcomes, such as low birthweight. There was a consensus that there was a need to supplement pregnant women with vitamins and minerals other than iron–folic acid and that combining different vitamins and minerals into one supplement would be an efficient approach. With this in mind, a multivitamin and mineral supplement designed for use by pregnant women in developing countries was developed and made available for the various trials through UNICEF. This multivitamin and mineral supplement was then tested in a series of 12 efficacy and 6 effectiveness trials covering 12 countries and spanning 3 continents—Asia, Latin America, and sub-Saharan Africa. The overall objective of these trials was to determine whether the use of a multivitamin and mineral supplement in pregnancy could not only improve critical outcomes such as birthweight but also improve adherence to the supplements in pregnancy, improve micronutrient status beyond anemia, increase gestational age at birth, and reduce the number of stillbirths and neonatal deaths. From a rights perspective, the idea was to take what women in industrialized countries and affluent women in developing countries take for granted as part of antenatal care and see how the same standard of care could be made available for women in developing countries.

Ten years later, with less than halfway to go before the Millennium Development Goal of 2015, what have we learned and what can we tell policy makers at the country level, international development agencies, and donors as a result of this investment? First, this systematic review of multiple micronutrient supplementation during pregnancy in developing countries contributes significantly to a body of evidence which shows that supplementing women in pregnancy can improve outcomes beyond anemia, including deficiencies of other vitamins and minerals and birthweight. The multivitamin and mineral supplement worked as well as, if not better than, the currently recommended iron–folic acid supplement in terms of reducing anemia. In the Copenhagen Consensus 2008 Perspective paper [1], Martorell goes on to conclude that "iron folic acid supplementation during pregnancy will not only improve iron status but also have a small effect on birth weight. Multiple micronutrient programs may yield significantly greater benefits on birth weight compared with iron." Second, the evidence once again confirms that adherence to supplement use is possible when supplements are made available in program settings and women are adequately counseled on their use. Third, in recent years evidence has come to light to show a positive effect on the functional and developmental milestones of children whose mothers were supplemented in pregnancy. A recent follow-up of Nepalese children whose mothers were supplemented with multiple micronutrients showed small improvements in weight and a decrease in peripheral adiposity after two years. Although the public health significance of this result is not yet known, the use of multiple micronutrient supplements by their mothers may have set these children onto a different development trajectory that could potentially mitigate the risk of chronic disease in adult life. Fourth, the results allude to how the multivitamin and mineral supplements could potentially have had a greater impact. Further improvements in anemia and birthweight might have been seen had women had access and started the use of the supplements in

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prepregnancy. There is a suggestion that increased amounts of vitamins and minerals may be needed for undernourished populations of pregnant women. Last, the results highlight what we already know about the importance of infection control in pregnancy and the importance of an integrated approach to pregnancy care. A recent commentary on prenatal micronutrient supplementation by Bhutta et al. [2] also supports the notion that optimal maternal nutrition can be achieved through various interventions and different strategies, and that the use of multiple micronutrient supplements adds a further benefit.

What we also learned is a new way of collaborating among researchers and policy makers that should and must be applied to ongoing questions of program relevance. As mentioned in the methods section of the paper on policy and program implications of this supplement [3], it is important for researchers to come together to collaborate to pool their intellectual resources and support the policy-making process. It is noteworthy how the policy and program members, particularly those who were funding the work, kept at arm's length with the researchers conducting the systematic review. We urge public health practitioners interested in finding answers to questions of public health importance to find similar ways of collaborating with the research community.

It is true that some important questions remain. Of great concern are the findings showing an increase, although not statistically significant, in the risk of early neonatal mortality associated with the use of multiple micronutrient supplements. This is also at odds with the findings of the large SUMMIT trial in Indonesia [4] that demonstrated the potential gains that could be made in reducing the burden of early infant mortality when multiple micronutrient supplements were provided in the context of strengthened health service delivery (i.e., deliveries by trained birth attendants and strong postnatal care). On this point there is consensus, and recommendations are available on the importance of strengthening health systems for maternal and newborn care. Furthermore, several initiatives are under way to increase the number of skilled health workers and improve the services that are available to women delivering at home.

Many individuals and institutions contributed at different times toward moving this work along, each further defining and shaping it along the way. The overall work was conducted under the aegis of the United Nations Sub-Committee on Nutrition (SCN), starting with the workshop on low birthweight in 1999 and concluding with the completion of the systematic review under SCN purview in 2008. We are grateful for the support of the US Agency for International Development (USAID) for funding the initial work through LINKAGES, the Government of Canada for providing UNICEF with the initial grant to support this research, the Micronutrient Initiative and Institute of Child Health for funding and hosting the first meeting of the investigators, and the US Centers for Disease Control and Prevention for their consistent support of the process and for funding this supplement. We also thank all of the members of the Systematic Review Team—Barrie Margetts, Lindsay Allen, Carine Ronsmans, and Caroline Fall—and their associates for the long hours dedicated to this work for very little remuneration. Last, thanks are due to UNICEF's Nutrition Section for diligently moving the process along over the last decade.

So what comes next? The World Health Organization will hopefully make a global recommendation that governments provide multiple micronutrient supplements instead of iron–folic acid, as is normal practice among women in many countries and especially among women of higher-income groups in countries where the trials were conducted. Such a recommendation will round off the current guidance on the use of multiple micronutrient supplements for pregnant and lactating women in emergencies. The international agencies, nongovernmental organizations, and donors must focus attention and resources on scaling up those interventions for which a solid evidence base is available and policy exists. The *Lancet* series on Maternal, and Child Undernutrition [5] also identified a number of doable interventions, including supplementary feeding of pregnant women with low BMI. There needs to be an increased focus on the health and nutrition needs of adolescent girls and on preventing teenage pregnancies. Where possible, efforts need to be stepped up to reach women before pregnancy, and on this front, there are some promising developments among countries in East Asia and the Pacific. Access to antenatal health care needs to improve, including the provision of maternal tetanus vaccination, antenatal supplements, deworming, and use of insecticide-treated bednets. And although many of these interventions are not directly measured as part of monitoring of Millennium Development Goals 4 and 5, there needs to be a system that allows monitoring of progress. Hopefully, with all this in place, we will not have to tell women in developing countries to wait another decade for the research to be perfected.

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Adherence and costs of micronutrient supplementation in pregnancy in a double-blind, randomized, controlled trial in rural western China

Lingxia Zeng, Hong Yan, Yue Cheng, Shaonong Dang, and Michael J. Dibley

Abstract

Background. *Efforts to determine the impact of prenatal multivitamin supplementation on birth outcome have been carried out in several developing countries. A review of factors that would impact the effectiveness of prenatal supplementation under normal field conditions is currently lacking and will be required for expanded supplementation programs. An efficacy trial of a multiple micronutrient supplement for pregnant women was conducted in rural western China, and additional information on side effects, rates of adherence, program inputs, and cost was also gathered.*

Objectives. *To examine reports of side effects and rates of adherence to prenatal multiple micronutrient supplementation in comparison with supplementation with folic acid and with iron–folic acid, and to describe inputs and costs associated with prenatal supplementation in China.*

Methods. *A cluster-randomized, double-blind, controlled trial was conducted in two rural counties in northwest China. All pregnant women in villages were randomly assigned to take daily supplements of folic acid, iron–folic acid, or a recommended daily allowance of 15 vitamins and minerals from enrollment until delivery. Information was collected from the women on side effects and adherence. Program inputs and costs of supplementation were tracked. Descriptive statistics were used for the analysis. The biological effectiveness of prenatal multiple micronutrient supplements is reported elsewhere.*

Results. *Less than 4% of women withdrew from the study because of side effects.*

Adherence to supplementation was high: the supplements were consumed on more than 90% of the days on which they were available for consumption. The mean number of supplements consumed was high at 165 capsules, and about 40% consumed the recommended 180 supplements during pregnancy.

Conclusions. *High adherence to a prenatal supplement schedule can be achieved when mothers have frequent contact with trained health workers and a reliable supply of supplements.*

Key words: Adherence, maternal supplementation, multiple micronutrients

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Background

Low adherence to iron supplementation in pregnancy has been widely reported and has been attributed to a variety of factors, including inadequate program support, insufficient delivery of services, and patient factors. These patient factors may include adverse side effects from the supplement and misunderstanding of the supplementation schedule [1].

Research has been conducted to determine the impact of prenatal multiple micronutrient supplementation on birth outcomes. UNICEF/United Nations University (UNU)/World Health Organization (WHO) [2] has recommended a formula for a multiple micronutrient supplement to be used in pilot programs among pregnant women in developing countries, and research has been conducted in multiple sites. As evidence mounts indicating a positive impact on birth size as well an improvement in maternal micronutrient status, development of larger multiple micronutrient supplementation programs is now planned.

Any efforts to expand multiple micronutrient supplementation will require information on the feasibility and effectiveness of prenatal supplementation under normal field conditions. Information on side effects and adherence will be required for defining communications needs and strategies. Information on inputs and costs will be required for program planning and design. Although a research study does not approximate a typical field setting, insights that will aid future programs can be gained, and needs for additional information can be identified.

To address the need for evidence from China on nutrient supplementation in pregnancy, a community-based, cluster-randomized, controlled trial was conducted in a disadvantaged rural population. The primary objectives of the trial were to assess the impact of iron–folic acid and multiple micronutrient supplements compared with folic acid alone during pregnancy on birth anthropometry, duration of gestation, and third-trimester maternal hemoglobin. Lingxia Zeng [3]. In addition to biological data, information on side effects and adherence was also gathered, as well as data on the inputs and costs associated with supplementation in China.

Background of the Ministry of Health program for maternal and child health care in China

China has made great progress in improving the health of women and children over the past 20 years [4]. Maternal mortality was reduced from 80 per 100,000 live births in 1991 to 48.3 per 100,000 live births in 2004 [5]. During these same years, mortality among children under 5 years of age dropped from 61 to 25 per 1,000 live births. With this marked improvement in maternal and child survival, China appears to be on track to meet the Millennium Development Goals [5].

However, as China has moved toward a market economy, inequities in access to health services have grown. Levels of insurance coverage have fallen dramatically, and health-care costs have greatly increased [6]. Management and financing of public health has become increasingly decentralized, and most of the spending on health now comes from local government finance. This has led to imbalances in public health inputs between urban and rural areas and among different regions [5]. Thus, 80% of China's health resources are currently concentrated in urban areas, while most of the maternal and child deaths occur in rural areas, particularly remote areas. In 2004, the maternal mortality rate was 3.2 times higher in rural areas than in urban areas and 7.7 times higher in inland areas than in coastal areas [5].

Without full government funding, institutions have become more profit oriented. Providers have begun to charge fees for some services and then use the revenue to cover nonpaid essential maternal and child health services and staff salaries [5]. This has resulted in maternal and child health institutions placing emphasis on treatment over prevention, and on paid over nonpaid services. This combination of modest government funding with client fees for maternal and child health services has negatively impacted the utilization of and access to maternal and child health services by low-income population groups [5].

Health care in China is provided through a three-tiered medical and health service network. In urban areas, the network consists of municipal hospitals, district-level hospitals, and community clinics. In rural areas, it consists of county hospitals, township health centers, and village clinics. Although rural doctors receive a limited amount of payment, depending on the financial status of the local government, they no longer receive their compensation from a rural collective economy, and they work essentially as private doctors.

These village doctors have 3 to 6 months of training and usually have their clinics in their homes. They act as maternal and child health workers at the village level, providing some basic antenatal, postpartum, and neonatal care as well as family planning education and, in remote areas, delivery services. Village doctors also are responsible for health education for their local community, supported by township maternal and child health staff [4].

Township health centers provide the second tier of services. Township health centers are usually staffed by doctors with 2 to 3 years of training and by midwives with 1 to 2 years of training. The centers have an average of 15 inpatient beds, and in the larger health centers cesarean section can be carried out [4]. In each township there is a staff person who specializes in maternal and child health care.

The third tier consists of services provided at the county and city level. Most obstetricians, gynecologists, and pediatricians work at the county or city level. At the county level there is a county hospital, such as a district general hospital, with around 300 beds, and a maternal and child health center.

The salaries of medical staff in the maternal and child health center and the maternal and child health staff at the township level are provided by the government. Most of the income of village-level doctors is from fees for services.

Since the 1980s, some programs supported by the Ministry of Health of China and by international nongovernmental organizations have focused on improving nutrition during pregnancy and decreasing vitamin and mineral deficiencies among the most vulnerable populations. The Chinese government is combining and adapting various approaches, including food fortification and supplementation, in order to improve the nutritional situation of pregnant women.

This micronutrient supplementation study was conducted in two poor rural counties located in Shaanxi Province of northwest China. Staff from the Chinese health system delivered the supplements and monitored outcomes. Medical staff from the health system received additional training and support, and women were provided with subsidized access to prenatal and delivery care.

Objectives

The objective of this analysis is to examine reports of side effects and rates of adherence for prenatal multiple micronutrient supplementation in comparison with supplementation with folic acid or iron–folic acid. In addition, this report describes the inputs and costs associated with prenatal multiple micronutrient supplementation in China. The primary study outcomes of birth anthropometry, duration of gestation, and maternal hemoglobin are reported.

Methods

A cluster-randomized, double-blind, controlled trial was conducted in two rural counties in Shaanxi Province of northwest China. All pregnant women in villages were randomly assigned to take daily supplements of folic acid, iron–folic acid, or a recommended daily allowance of 15 vitamins and minerals (United Nations International Multiple Micronutrient Preparation [UNIMMAP]) from enrollment until delivery [2]. The sample included all women in the counties who became pregnant between August 2002 and January 2006 who met the eligibility criteria and who provided oral informed consent. Women were ineligible if they were already taking supplements, had a serious illness, had an abnormal reproductive history, were planning to work outside the area, or were more than 28 weeks pregnant.

This study was approved by the Human Research Ethics Committee of the College of Medicine, Xi'an Jiaotong University (No 2002001) and the Ministry of Health, China. All women gave informed verbal consent.

Village doctors, with active support from the township maternal and child health care workers, conducted active surveillance for pregnancy among women of reproductive age in order to recruit participants. Consenting women identified as likely to become pregnant were visited each month to assess their pregnancy status. Women with periods delayed by more than 5 days had a urine pregnancy test, and confirmed pregnancies were reported to the township maternal and child health worker. Pregnancies among women in townships or counties were passively detected at antenatal clinics in local health facilities. The total survey sample was 5,828, with 2,017 women living in 178 villages in the folic acid group, 1,912 women living in 183 villages in the iron–folic acid group, and 1,899 women living in 170 villages in the group receiving multiple micronutrients.

The same treatment was given to all pregnant women identified in a given village. The multiple micronutrient supplements contained the recommended dietary allowance (RDA) for 15 vitamins and minerals and included 30 mg of iron. The iron–folic acid supplement contained 60 mg of iron and 400 μg of folic acid. The folic acid supplement contained 400 μg of folic acid.

At enrollment, each woman received 15 capsules in blister strips and was instructed to take one capsule daily. The village doctor visited each woman every two weeks to distribute additional supplements and collect used blister strips. The number of remaining capsules was recorded. To estimate adherence, the number of supplements distributed and mean number of supplements consumed during the pregnancy (including women who later had fetal losses) was calculated.

Side effects were self-reported by the study participants. Reports were collected by village doctors when they collected the blister strips or by the clinic physicians in counties.

Descriptive statistics were used to identify program inputs. Program administrators tracked direct costs of the project.

Inputs the project provided

Given the current market orientation of China's maternal and child health services, in order for study participants to have equal access to maternal and child health services, allow for measurement of birth outcomes, and ensure high rates of adherence to supplementation, a series of additional inputs was required. In addition to training for service providers and free supplements, access to antenatal services (which currently requires user fees) was provided for free. Subsidies were also provided to women to encourage them to deliver their babies in the hospital.

The multiple micronutrient supplementation project provided staff with training in order to ensure that the project was implemented smoothly. Staff at different levels received different training based on the skills and duties required.

Training for village doctors included how to carry out active surveillance of pregnancy, how to distribute the antenatal supplements, and how to report the early termination of pregnancy. The training for maternal and child health staff at the hospital level focused on skills for antenatal and postnatal care and how to identify a high-risk pregnancy. Training was conducted by the research staff.

The antenatal supplements were distributed by the local maternal and child health system. The supplements were given to all pregnant women enrolled in the trial from the time of enrollment until the time of delivery or termination of pregnancy. Village doctors or township maternal and child health center staff visited the women every 2 weeks to distribute the supplements and to collect the remaining unused supplements. The frequency of visits was reduced to once a month if the woman understood the supplementation regime and demonstrated high adherence. If the village doctor was unable to distribute the supplements reliably, the township maternal and child health staff took over this task.

In order to increase adherence to supplementation and to antenatal and delivery care, the project covered the cost of three antenatal care visits and one postnatal care visit at 42 days after delivery. The first free antenatal care visit was conducted at enrollment, the second at 18 weeks of gestation, and the third at 32 weeks of gestation. Normally, women would have to pay for these visits, and therefore they often did not receive antenatal care on this regular basis.

During the visits, women were asked about complications and received a physical examination that included blood pressure and weight measurement. Hemoglobin was measured at the third antenatal check. In addition, the woman received a subsidy of 30 RMB (about US$4) if she delivered the baby at the hospital. The project also provided additional payments to the doctors who were responsible for the prenatal care and delivery of the women enrolled in the trial.

Members of the project team from Xi'an Jiaotong University were responsible for project supervision and monitoring. The project team was composed of an epidemiologist, a statistician, data management workers, a pediatrician, an obstetrician, and graduate students. Members of the project team visited the field monthly, conducted a routine project meeting with the local maternal and child health staff, reported progress, and dealt with the problems that occurred during project implementation. The project team also visited every township and selected village doctors in order to ensure that the field procedures were followed correctly. The team provided intensive supervision that would normally not have taken place in a government supplement distribution program. Xi'an Jiaotong University research team members also reinterviewed randomly selected pregnant women enrolled in the trial to recheck the data collected (**fig. 1**).

Results

Adherence to supplementation by subjects

The dropout rates (withdrawals and lost to follow-up) among the total of 5,828 women in the study were low. Only 2.8% of women withdrew because of self-reported side effects of folic acid, 3.9% because of side effects of iron–folic acid, and 4.2% because of side effects of multiple micronutrients (**table 1**). The rate of withdrawal because of reported side effects was significantly higher in the iron–folic acid group and the group receiving multiple micronutrients than in the group receiving folic acid only ($p < .05$), a result suggesting that the iron in the supplements given to the two former groups may have caused more side effects. However, the rate of dropout because of reported side effects did not differ between the iron–folic acid group and the group receiving multiple micronutrients, even though the iron–folic acid group received twice the amount of iron as the group receiving multiple micronutrients. The side effects reported most frequently included nausea (47% of those who withdrew because of side effects), severe gastrointestinal symptoms (34%), and vomiting (16%), with no differences between the supplement groups.

Distribution of consumption of supplements

Of the 4,815 women who remained in the study**,** 41% started taking supplements during the first trimester

TABLE 1. Surveillance outcomes in the three treatment groups—no. (%)

Outcome	Folic acid	Iron–folic acid	Multiple micronutrients	Total
Dropouts				
Total dropouts	101 (5.0)	161 (8.4)	150 (7.9)	412 (7.1)
Lost to follow-up	29 (1.4)	58 (3.0)	46 (2.4)	133 (2.3)
Total withdrew from project	72 (3.6)	103 (5.4)	104 (5.5)	279 (4.8)
Withdrew because of side effects	56 (2.8)	74 (3.9)	79 (4.2)	209 (3.6)
Early termination of pregnancy	211 (10.5)	186 (9.7)	204 (10.7)	601 (10.3)
Spontaneous abortion	136 (6.7)	108 (5.7)	121 (6.4)	365 (6.3)
Induced abortion	73 (3.6)	75 (3.9)	78 (4.1)	226 (3.9)
Termination for medical reasons	2 (0.1)	3 (0.2)	5 (0.3)	10 (0.2)
Birth	1,705 (84.5)	1,565 (81.9)	1,545 (81.4)	4,815 (82.6)
Total	2,017	1,912	1,899	5,828

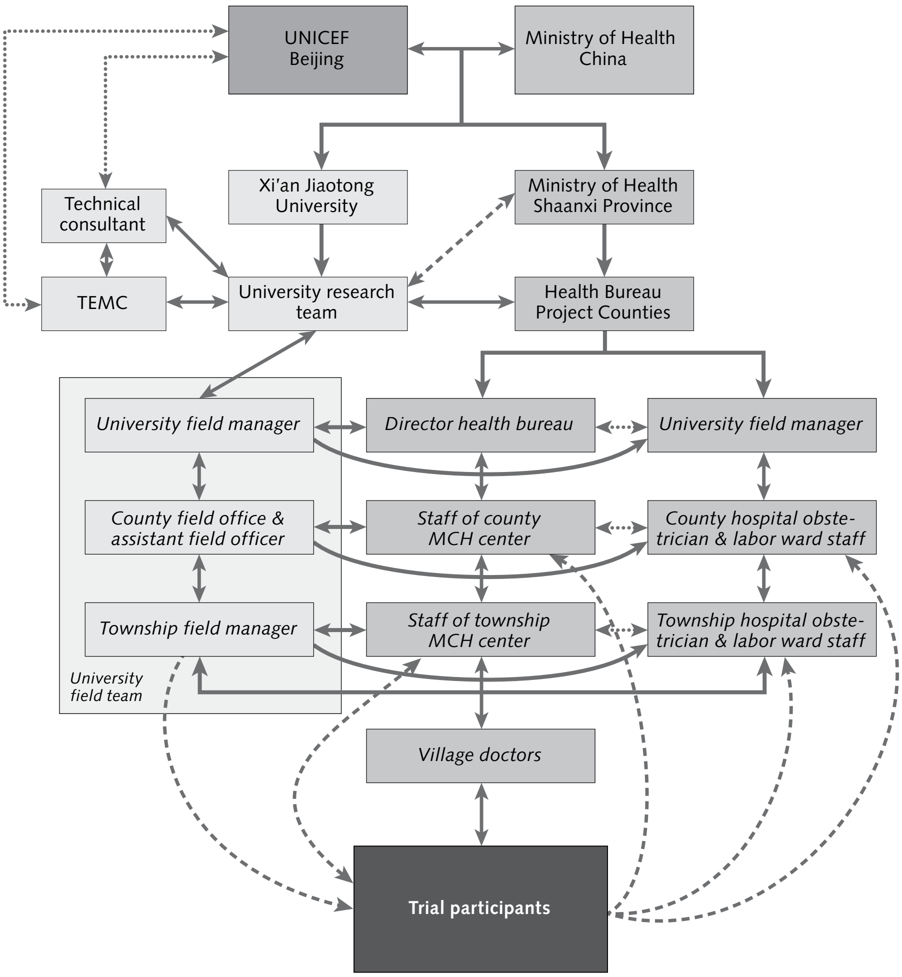

FIG. 1. Organizational structure of micronutrient supplement project in Xi'an study. MCH, Maternal and Child Health; TEMC, Tertiary Education Management Conference.

(**table 2**). Only about 6% delayed starting supplements into the third trimester. The mean time at which the women began to take the supplements was the 14th week of gestation.

The mean number of supplements consumed during pregnancy was 165 or 166 for each group. About 40% of the women consumed the WHO-recommended number of 180 supplements during pregnancy [7].

The rates of adherence were high and were similar for the three treatment groups. Adherence is defined as the percentage of days on which supplements were consumed among all the days on which they were available for consumption. The mean adherence was 93% among those taking folic acid, 92% among those taking iron–folic acid, and 93% among those taking multiple micronutrients. The rate of adherence was more than 75% among more than 90% of women in all three groups.

Program costs

The cost structure of this micronutrient supplementation research program was estimated based on the report of the financial management system of Xi'an Jiaotong University. The total cost of the program was US$315,805, but much of this included the cost of the research component, estimated to be about one-third of the total costs (although this may be an overestimate, given that the amount of training and supervision was probably higher than would normally be needed to improve prenatal care because of the data collection required of maternal and child health personnel). For details of data collection instruments and topics covered in training for different staff level in this trial, see **tables 3** and **4**.

Given this caveat, an estimate can be made of the costs of this program. After deletion of the costs related to research staff, the total cost of improving antenatal, delivery, and postnatal care is estimated at US$217,000

TABLE 2. Adherence to supplementation and number of supplements taken during pregnancy according to treatment group[a]

Variable	Folic acid	Iron–folic acid	Multiple micronutrients
No. of women who completed pregnancy	1,705	1,565	1,545
Adherence—no. (%) of women			
0%–25%	9 (0.6)	16 (1.0)	18 (1.2)
26%–50%	24 (1.4)	29 (1.9)	32 (2.1)
51%–75%	95 (5.6)	110 (7.0)	88 (5.7)
76%–100%	1,577 (92.5) *n* = 1,705	1,410 (90.1) *n* = 1,565	1,407 (91.1) *n* = 1,545
Mean ± SD adherence—%	93.4 ± 12.7	91.9 ± 14.8	92.6 ± 14.9
No. of supplements consumed—no. (%) of women			
< 90	105 (6.2)	85 (5.4)	106 (6.9)
91–119	181 (10.6)	160 (10.2)	154 (10.0)
120–179	684 (40.1)	638 (40.8)	630 (40.8)
≥ 180	735 (43.1) *n* = 1,705	682 (43.6) *n* = 1,565	655 (42.4) *n* = 1,545
Mean ± SD no. of supplements consumed	165 ± 44	166 ± 44	165 ± 45
Week of gestation when supplementation began—no. (%) of women			
< 12	697 (40.9)	644 (41.2)	599 (38.8)
12–23.99	894 (52.4)	838 (53.6)	848 (54.9)
24–28	114 (6.7) *n* = 1,705	83 (5.3) *n* = 1,565	98 (6.3) *n* = 1,545
Mean ± SD week of gestation when supplementation began	13.8 ± 5.7	13.6 ± 5.6	13.9 ± 5.6

a. Adherence is defined as the number of days on which supplements were consumed divided by the number of days on which supplements were available for consumption, expressed as a percentage.

for 5,416 women, or US$40 per woman. Only 22% of the costs (US$8.80 per pregnancy or US$.05 per day based on the mean consumption of 165 supplements in pregnancy) were for the supplements (**fig. 2**), including purchase of the capsules and distribution, which included transportation from Beijing to Xi'an and from the local maternal and child health station to the townships and villages. Twenty-seven percent of the total cost was for fees for antenatal and postnatal care for all the participants and the subsidy for hospital delivery. In a setting with free access to such care, these costs would not be incurred. Since the supplements were provided to women free of charge, no costs were recovered.

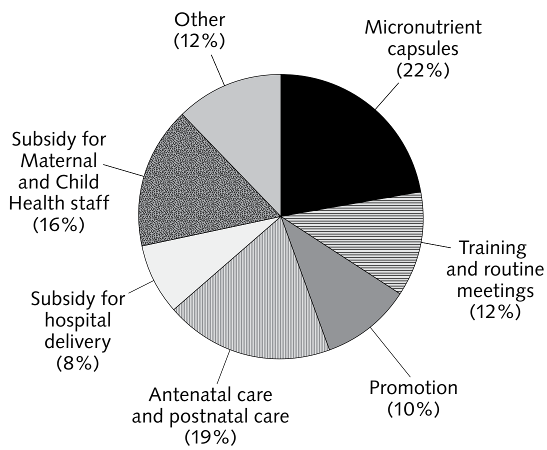

FIG. 2. Percentage distribution of costs of micronutrient supplement project (excluding research costs) in Xi'an study

Discussion

The rates of adherence to micronutrient supplementation in this project, about 90%, were higher than those in many other studies, probably because of the intensive follow-up of pregnant women, the subsidies provided to the health-care providers, and the training and supervision of the health workers by the research staff. About 40% of the women consumed the recommended number of 180 or more supplements in pregnancy. A study in Nepal showed that pregnant women started to take supplements at 11 weeks of gestation on average, and the mean rates of adherence were 72% to 76% among different treatment groups [8]. The adherence

TABLE 3. Trial forms

Name of form	Form code	Person(s) who fulfills this task and completes this form	Data entry
Data collection forms			
Consent form and information sheet	C	Project MCH worker	No
Pregnancy care record book		Project MCH worker/hospital antenatal care staff/hospital delivery care staff	Yes
Pregnancy registration form	R	Project MCH worker	Yes
Baseline survey form	B	Project MCH worker	Yes
Record of first antenatal care exam	C	Project MCH worker	Yes
Record of second antenatal care exam	D	Project MCH worker	Yes
Record of third antenatal care exam	E	Project MCH worker	Yes
Early termination of pregnancy form	F	Project MCH worker	Yes
Records from delivery to discharge from hospital	G	Project MCH worker	Yes
Record of delivery (another newborn)	H	Project MCH worker	Yes
Record of postpartum visit at 6 wk	I	Project MCH worker	Yes
Record of death	J	Project MCH worker	Yes
Record of pregnancy outcome form	O	Village doctor/hospital delivery care staff	No
Record of supplement distribution	S	Village doctor/project MCH worker	Yes
Food-frequency questionnaire	AC	Project MCH worker	Yes
Data management forms			
Pregnancy identification form	P	Village doctor/project MCH worker	No
Delivery log book	L	MCH/township hospital staff	No
Dispatch form	D	Project fieldworker	No
Field report form	R	Village doctor/project MCH worker	No

MCH, Maternal and Child Health

TABLE 4. Topics covered in multiple micronutrient training for different staff levels

Staff level	Topics covered in training
Maternal and child health and county hospital staff	Project field procedures and requirements for completing the pregnancy care record book and delivery log book Skills of maternal health care, including antenatal care and postnatal care Identification of the high-risk pregnancy Management of the newborn and obstetrical emergencies Maternal and newborn anthropometry
Township health center staff	Project field procedures and requirements for completing the pregnancy care record book and other forms Skills of maternal health care, including antenatal care and postnatal care Identification of the high-risk pregnancy Hemoglobin concentration measurement by HemoCue Maternal and newborn anthropometry Consent procedure for participants
Village doctors	Urine test for early pregnancy identification Health education about prenatal care and hospital delivery Supplementation distribution and compliance monitoring procedures

rate was higher in our study than the rate found by a project in China administering folic acid for the prevention of neural tube defects, with adherence of 78% in northern areas and 81% in southern areas [9].

The rates of adherence to supplementation are much lower in normal health programs, as shown by the results of Demographic and Health Surveys in many developing countries, where most women do not consume any iron tablets in pregnancy and low proportions of women consume the recommended number of 180 supplements. For example, in Nepal, 41% of pregnant women did not take any iron in pregnancy, and only 7% consumed 180 or more tablets [10]. In our study, additional inputs to normal maternal and child health programs resulted in high rates of adherence. The capsules were distributed directly to women, the health workers were trained and supervised, and the women were encouraged to participate in antenatal care through payment to cover the costs of such care.

The low rate of dropouts due to reported side effects in all three groups refutes the view that women do not consume supplements because of side effects [7]. Ensuring the supply of micronutrients, adequate training and supervision of health workers, and attendance at antenatal care visits is needed in order to enhance supplement usage.

At present, the cost of delivery at the hospital is included in the list of costs to be reimbursed by the Cooperative Medical Care System in China; however, often women need an additional subsidy as an incentive or to cover their transportation costs to the facility. Some programs supported by the Ministry of Health of China are trying to include prenatal and postnatal care in the list of costs to be reimbursed by the Cooperative Medical Care System. This would be beneficial for women's health and improve infant outcomes, as well as providing a means to increase supplement use in pregnancy. But such services need funds, and as shown in this study, although cost calculations are crude, the estimate of the additional services needed is about US$40 per woman. Only a small proportion (US$8.80) of this is for purchase and distribution of supplements. This cost would probably be reduced with bulk purchases.

Free micronutrient supplements are key to improving nutritional status during pregnancy in rural areas. Given that the use of multiple micronutrients improves the woman's nutritional status (reducing anemia) and the outcome of pregnancy (improving birthweight) in China and elsewhere, this cost is justifiable.

Conclusions

High adherence to a prenatal micronutrient supplement schedule can be achieved when all mothers have frequent contact with trained health workers and a reliable supply of supplements. Few women stopped taking supplements during pregnancy. Because subsidies for the health sector encouraged antenatal care, the women were visited in their homes for resupply and supplements were provided free of charge. The next step is to expand the use of multiple micronutrients in pregnancy and attempt to find ways to reduce the costs of such programs, perhaps through provision of a supply of supplements at the first antenatal care visit (rather than every 2 weeks), sale of supplements, and behavior change communication to encourage their use.

Acknowledgments

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Preventing low birthweight through maternal multiple micronutrient supplementation: A cluster-randomized, controlled trial in Indramayu, West Java

Sunawang, Budi Utomo, Adi Hidayat, Kusharisupeni, and Subarkah

Abstract

Background. *Micronutrient deficiencies may contribute to a higher incidence of low birthweight (LBW). UNICEF/United Nations University/World Health Organization jointly proposed a formulation for a multiple micronutrient supplement for pregnant women, and several effectiveness trials were conducted to assess its impact.*

Objective. *To evaluate the efficacy of prenatal multiple micronutrient supplementation for improving birth size, pregnancy outcome, and maternal micronutrient status in comparison with iron–folic acid supplementation.*

Methods. *We carried out a cluster-randomized, controlled trial in Indramayu, Indonesia, involving 843 pregnant women. Of these, 432 received multiple micronutrients and 411 received iron–folic acid. Fieldworkers visited the women daily to observe supplement consumption and record fetal loss and mortality.*

Results. *The mean number of supplements consumed during pregnancy and 30 days postpartum was high (136 in the group receiving multiple micronutrients and 140 in the iron–folic acid group). The women consumed the supplements on average 5 days per week. Although there were no significant differences between the groups in the percentage of infants with LBW, there was a trend toward a lower incidence of LBW in the group receiving multiple micronutrients (6.3% vs. 7.3%), and the mean birthweight was 40 g higher in the group receiving multiple micronutrients than in the iron–folic acid group, although the difference was not significant. Among those who consumed 90 or more supplements during pregnancy, women taking multiple micronutrients had a 3.3% combined rate of miscarriage, stillbirth, or neonatal death, as compared with 6.9% for those taking iron–folic acid only ($p < .049$). The anemia rates in the two groups were similar after supplementation, even though the amount of iron in the multiple micronutrient supplement was half that in the iron–folic acid supplement. Serum retinol was higher in the group receiving multiple micronutrients.*

Conclusions. *Multivitamin supplementation use among pregnant women is as effective as iron–folic acid in improving anemia status and appears to have other benefits for maternal and child nutritional status.*

Key words: Abortion, birth size, low birthweight, maternal supplementation, multiple micronutrients, neonatal death, stillbirth

Background

Low birthweight (LBW) is associated with many adverse effects. LBW increases the risk of perinatal mortality by more than 10-fold and is associated with four times the risk of postneonatal mortality [1, 2]. LBW is linked with decreased intelligence, poor school performance, decreased ability to compete in the workplace, and increased poverty [3–5]. When they reach adulthood, LBW babies are more likely to suffer from degenerative diseases, including hypertension, diabetes, and atherosclerosis [6–10].

Dietary intake and micronutrient status studies show that maternal micronutrient deficiencies in iron, vitamin A, zinc, vitamin B_{12}, iodine, and folate are widespread and have a negative impact on pregnancy outcomes. Current data suggest a plausible role for iron, zinc, and vitamin A in improving birth outcomes, including birthweight [11–13].

Although it is common for women in industrialized countries to take multivitamin supplements during pregnancy, until recently a multiple micronutrient supplement specifically designed for use by women in developing countries has not existed. In 1999, UNICEF,

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the World Health Organization (WHO), and the United Nations University (UNU) jointly proposed a composition of a multiple micronutrient supplement for pregnant women in developing countries to be used in efficacy and effectiveness trials to assess its impact—the United Nations International Multiple Micronutrient Preparation (UNIMMAP). The contents of the supplement are shown in the Huy et al. article in this journal supplement [14]. A number of issues related to maternal micronutrient supplementation needing further investigation were identified. UNICEF/UNU/WHO recommended further study of indicators related to birth outcome, including assessment of anthropometry at birth. It was also recommended that pregnancy outcome as well as biochemical markers of the nutritional status of the mother be investigated [12].

In order to evaluate the effect of the UNICEF/UNU/WHO proposed supplement on these outcomes, this study was carried out from May 2001 through September 2003 in Indramayu, Indonesia.

Objective

The objective was to evaluate the effect of supplementation with the recommended multiple micronutrient supplement in comparison with iron–folic acid on birth size, pregnancy outcome, and micronutrient status in women.

Methods

Study population

Two subdistricts of Indramayu District in the West Java Province of Indonesia were chosen to represent an average district in terms of economic development and health status. Previous studies indicated a high prevalence of anemia among pregnant women in this study area [15, 16]. These two subdistricts have populations of 67,082 and 52,135, include 25 villages, and are divided into 157 hamlets.

The sample size was calculated based on 80% study power to be able to detect a 50% reduction in the incidence of LBW among the treated group as compared with the control group and allow a type I error at $\alpha = .05$ for a one-sided test. We used 0.1 as the estimated proportion of LBW among the control group in the sample calculation [15]. The sample was then increased to allow for dropout due to rejection or migration and adjustment for the design effect due to randomization according to dwelling block. The total sample required was 428 for each group [17].

Registration of pregnant women took place from May 2001 through December 2002. The last woman in the sample gave birth in August 2003. Pregnancy status was confirmed with a dipstick pregnancy test (Acon Laboratories), and then the woman was asked to recall the first day of her last menstrual period. Only those intending to remain in the study location until giving birth were recruited. Women suffering from potentially confounding illnesses, including diabetes, coronary heart disease, and tuberculosis, were excluded from the study. All women were required to provide written informed consent in order to participate. Ethical clearance for the study protocol was obtained from the Ethical Committee of the University of Indonesia, Depok.

Study design

The design of the study was a randomized community trial in which a cluster of dwellings served as the unit for randomization. We restructured the 157 hamlets into 160 dwelling clusters to obtain an equal number of households in every cluster and clear physical boundaries between clusters. These 160 clusters (and the pregnant women living within them) were randomly assigned to 4 blocks of 40 clusters each. Two of the four blocks were part of an effectiveness trial (not reported in this paper), and women in the other two blocks received either the multiple micronutrient supplement or iron–folic acid.

The fieldworkers carried out intensive surveillance to identify all pregnant women in the clusters, checking mothers at religious gatherings and *posyandu* (growth promotion and monitoring posts) or directly contacting the traditional birth attendants in order to identify any new pregnant women. There were 843 eligible women who were located this way and enrolled in this study; 432 women in 40 clusters were allocated to the group receiving multiple micronutrients and 411 in the other 40 clusters were allocated to the iron–folic acid group.

This study had a single-blind design, since the supplements for the treatment and control groups looked different physically. However, participants residing in each cluster received the same supplement, so they were not aware that participants in other clusters received a different supplement. Supplements were given from the time of enrollment at 12 to 20 weeks of gestation and continued up to 30 days postpartum.

The multiple micronutrient supplements contained the recommended daily allowance of 15 micronutrients according to the UNICEF/UNU/WHO recommended formula, including 30 mg of ferrous fumarate. They were supplied by UNICEF Jakarta and were produced by PT SOHO Pharmaceutical Company, Jakarta, to ensure that the supplement met Muslim *hallal* standards [12]. The iron–folic acid supplements contained 60 mg of elemental iron as ferrous sulfate and 0.25 mg of folic acid and were purchased from PT Kimia Farma, Jakarta.

To ensure that the participants received the full recommended dosage of the supplement, the women in the intervention and control groups were visited daily (except Sunday) and the supplement was dispensed to them by the fieldworkers, with consumption of the supplements observed. The consumption of vitamins and minerals dispensed from other sources was assessed by daily direct monitoring. Local health centers were advised not to dispense redundant iron–folic acid tablets to those women already receiving supplements from the study. Women were advised to discontinue the use of vitamins and minerals from other sources, and any additional use was recorded. If the woman did not discontinue use of additional supplements, she was excluded from the analysis. The fieldworkers also encouraged all study participants to receive antenatal care checks at their local health centers and recorded their antenatal care visits.

Measurement of outcomes

Under the guidance of local health service staff, the fieldworkers established a communication network with local traditional birth attendants in order to identify any woman giving birth and to immediately measure the newborn. Birthweight was measured by a spring-type infant scale (Misaki, Japan) to the nearest 50 g. Birth length was measured with a WHO standard length board [18] to the nearest 1 mm. Head and chest circumferences were measured with a fiberglass measuring tape (Butterfly, Japan) to the nearest 1 mm. All measurements were taken twice. If different results were obtained, a third measurement was taken and the average value was recorded. The measurement tools were strictly calibrated every morning. We used standard weight and standard length instruments produced by the Metrology Office for routine calibration of scales and length measurements.

Venous blood specimens and urine samples were taken randomly from 25% of the subject women at the beginning of the study and repeated again at approximately 8 months of gestation by phlebotomists from the National Nutrition Research Institute in Bogor. The blood specimens were analyzed for hemoglobin, serum ferritin, serum zinc, and serum retinol; the urine was analyzed for iodine concentration. Analyses were performed in the certified laboratory of the Bogor Nutrition Research Institute. The hemoglobin concentration in the peripheral blood was measured directly with a hemoglobin reader (HemoCue) in all women at baseline and at 8 months of gestation.

Data on compliance and side effects of supplementation as well as morbidity and fetal loss were collected from weekly visits. Miscarriage or spontaneous abortion was defined as termination of pregnancy before 28 weeks; stillbirth was defined as fetal loss from 28 weeks or later up to birth, but without sign of life. We defined neonatal death as death of a live-born infant up to 28 days after birth. There was no in-depth effort to identify the cause of death by verbal autopsy. Reports on fetal loss and neonatal death were double-checked directly with the mothers by the field coordinators.

Analytical methods

We excluded all twins from the analysis of birthweight and pregnancy outcome. Infants whose birth size was measured later than 3 days after birth were excluded from the analyses of birthweight. We also excluded any outcomes of pregnancy among women who migrated to other districts.

Characteristics of the subjects at baseline were compared between the intervention and control groups to check whether randomization was successful. Pregnancy outcomes and confounding factors were compared across treatment groups in terms of mean differences for numeric variables or odds ratios for categorical variables. Rates of miscarriage, stillbirth, and neonatal death were compared between groups. Because of the small number of events, these categories

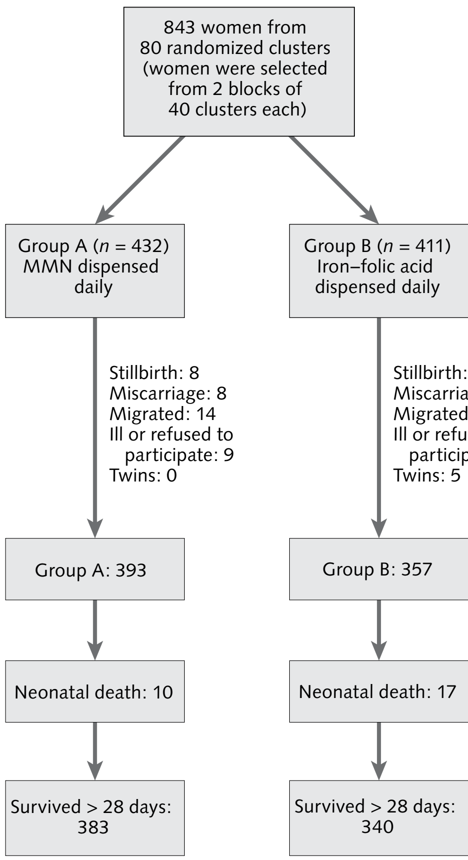

FIG. 1. Schematic diagram of study subjects from recruitment to the end of the study. MMN, multiple micronutrients

were then combined into one pregnancy outcome category for analysis. The impact of supplementation on pregnancy outcome was also analyzed for the subgroups of women consuming fewer than 90 supplements compared with those consuming 90 or more supplements.

Results

Recruitment was stopped after recruitment of 1,737 pregnant woman, which was enough to yield the calculated sample size. Of these 1,737 women, 43 declined to participate and 1,694 agreed to take part in the two multiple micronutrient studies. There were 843 pregnant women in this study, while the remaining 851 pregnant women participated in a parallel effectiveness study in which women were given a month's supply of supplements rather than being given them daily. Of the 843 women in this trial, 51 migrated or dropped out of the study because of illness or refusal to participate, and 37 pregnancies resulted in miscarriage or stillbirth (**fig. 1**).

A total of 393 women in the group receiving multiple micronutrients and 357 in the group receiving iron–folic acid (89% of initial participants) delivered a live-born infant who was measured by the fieldworkers. Five of these women delivered twins and were thus excluded from the analysis. Forty-four percent of infants were measured on the day of birth, 93% within 2 days after birth, and 97% within 3 days after birth.

There were no major differences between the two groups in baseline demographic characteristics (**table 1**). On average, the women were 25 or 26 years of age, and 43% were primiparous. There were no differences between the group receiving multiple micronutrients and the group receiving iron–folic acid in mean weight (51.2 and 51.0 kg, respectively) or height

TABLE 1. Baseline characteristics of the women

Characteristic	Multiple micronutrients (*n* = 432)	Iron–folic acid (*n* = 411)	*p*
Mean ± SD age (yr)	25.4 ± 6.1	26.1 ± 6.5	.142
Age (%)			.248
≤ 19 yr	18.5	14.6	
20–29 yr	56.0	56.7	
≥ 30 yr	25.5	28.7	
Parity (%)			.318
0	44.0	41.6	
1	27.5	27.3	
2	15.5	17.3	
3	7.4	5.4	
≥ 4	5.6	8.5	
Mean ± SD prepregnancy height (cm)	151.5 ± 5.2	151.3 ± 4.9	.742
Mean ± SD prepregnancy weight (kg)	51.2 ± 8.8	51.0 ± 9.7	.768
Maternal BMI (%)			.580
≤ 18.50	10.5	13.9	
18.60–22.00	43.4	39.5	
22.01–24.99	25.8	25.4	
25.00–29.99	16.9	18.1	
≥ 30.0	3.3	3.0	
Mean ± SD height of father (cm)	162.9 ± 5.9	162.7 ± 5.1	.703
Maternal schooling (%)			.682
None	8.8	10.0	
1–5 yr	23.1	23.1	
6–12 yr	67.8	66.2	
≥ 13 yr	0.2	0.7	
Mean ± SD gestational age at baseline (days)	100.7 ± 11.5	100.5 ± 11.9	.962
Started supplements in 1st trimester[a] (%)	4.62	6.8	.435

BMI, body mass index
a. First trimester is defined as ≤ 12 weeks of pregnancy.

(151.5 and 151.3 cm, respectively). Eleven percent of the women had chronic energy deficiency (body mass index [BMI] ≤ 18.5), 20% were overweight or obese (BMI ≥ 25.0), and 3.0% were obese (BMI ≥ 30.0).

The mean gestational age at baseline, calculated from recall of the last menstruation date, was 101 days (14.4 weeks) in both groups (**table 1**). Less than one-tenth of women started supplementation in the first trimester in both groups.

Compliance with daily supplements was high in both groups, with a mean of 136 and 140 supplements consumed in the group receiving multiple micronutrients and the group receiving iron–folic acid, respectively, consumed during pregnancy and in the first 30 days postpartum. The distribution of the total number of tablets consumed is shown in **table 2**. About 70% of the women in both groups consumed at least 120 supplements. The women in the group receiving multiple micronutrients and the group receiving iron–folic acid consumed the supplements for a mean of 68% and 71% of days of participation, respectively. Few side effects were reported, and there were no significant differences between the groups in the incidence of side effects.

The mean gestational age at birth (**table 3**) did not differ between groups, at 38.1 weeks for the group receiving multiple micronutrients and 38.0 weeks for the iron–folic acid group (p = .61).* The mean birthweight was 3,094 ± 438 g in the group receiving multiple micronutrients and 3,054 ± 419 g in the iron–folic acid group (p = .21). The prevalence of LBW was 6.3% and 7.3%, respectively (p = .667). Birth length and head circumference also did not differ significantly between the two groups.

The rates of miscarriage, stillbirth, and neonatal death did not differ between the treatment and the control group (**table 4**). However, when all three categories are combined, women receiving multiple micronutrient supplements appeared to benefit over the control group at the borderline of significance, with p = .09 (OR = 0.6; 95% CI, 0.37 to 1.04). Further stratification analysis showed that the number of supplements consumed had a differential impact on fetal loss and neonatal death. Women in the group receiving multiple micronutrients who consumed 90 or more supplements had a significant reduction in the combined risk of fetal loss or neonatal death (OR = 0.45; 95% CI, 0.22 to 0.95) as compared with women in the control group. The impact was not significant among women consuming fewer than 90 supplements (OR = 0.72; 95% CI, 0.32 to 1.59).

Although the rate of anemia was higher in the group receiving multiple micronutrients at baseline, the trend in anemia rates by the third trimester was similar in the two groups (**fig. 2A**). Comparisons of baseline serum levels measured during the last trimester showed that the mean levels of hemoglobin (**fig. 2B**) and zinc (**fig. 3A**) declined significantly in both groups (p < .05); however, serum retinol improved in the group

* Only those with a gestational age at birth between 27 and 45 weeks were included in the analysis of gestational age at birth.

TABLE 2. Consumption of supplements during pregnancy and the first month after delivery

Variable	Multiple micronutrients (n = 392)	Iron–folic acid (n = 356)	p
Mean ± SD no. of supplements consumed	136 ± 44	140 ± 40	.171
No. of supplements consumed (%)			.480
< 90	16.1	12.1	
90–119	14.8	14.9	
120–179	54.3	56.9	
≥ 180	14.8	16.1	
Mean adherence[a] (%)	68	71	.142

a. Adherence is defined as the number of supplements consumed divided by the days women could have consumed the supplements, calculated from the day of recruitment up to 30 days postpartum, presented as a percentage.

TABLE 3. Impact of supplements on birth size and gestational age[a]

Outcome	Multiple micronutrients	Iron–folic acid	Difference (95% CI)	p
Gestational age at delivery (wk)	38.1 ± 3.2 (n = 395)	38.0 ± 3.2 (n = 364)	0.119 (−0.34 to 0.58)	.611
Birthweight (g)	3,094 ± 438 (n = 384)	3,054 ± 419 (n = 341)	40.47 (−22 to 103)	.205
LBW[b] (%)	6.3	7.3	0.84 (0.47 to 1.50)	.667
Birth length (cm)	47.6 ± 2	47.45 ± 2.1	0.14 (−0.16 to 0.45)	.346
Birth head circumference (cm)	33.25 ± 1.4	33.2 ± 1.3	0.04 (−0.16 to 0.23)	.710

a. Plus–minus values are means ± SD.
b. Low birthweight (LBW) is defined as < 2,500 g.

TABLE 4. Impact of supplements on fetal loss and neonatal mortality

Outcome	Multiple micronutrients (*n* = 432	Iron–folic acid (*n* = 411)	OR (95% CI)	*p*
Miscarriage (< 28 wk)	8 (1.9%)	13 (3.2%)	0.57 (0.23 to 1.39)	.304
Stillbirth (28 wk to delivery)	8 (1. 9%)	8 (2%)	0.90 (0.35 to 2. 5)	1.000
Neonatal death (< 28 days after birth)	10 (2.3%)	17 (4.2%)	0.54 (0.2 to 1.2)	.181
Total miscarriage, stillbirth, or neonatal death				
All women	26 (6.0%)	38 (9.4%)	0.60 (0.37 to 1.04)	.091
Women who consumed < 90 supplements	15 (16%)	15 (20.8%)	0.72 (0.32 to 1.59)	.545
Women who consumed ≥ 90 supplements	11 (3.3%)	23 (6.9%)	0.45 (0.22 to 0.95)	.049

receiving multiple micronutrients ($p = .08$) but not in the control group (**fig. 3B**). Iodine levels increased in both groups.

Discussion

This efficacy study attempted to assess the impact of supplementation with multiple micronutrients and iron–folic acid on birthweight, pregnancy outcome, and micronutrient status in women. By distributing supplements directly to women in their homes and observing their intake of the supplements, high rates of adherence to supplementation were obtained. Nearly three-quarters of the women in both groups consumed more than 120 supplements during pregnancy and the first 30 days postpartum. On the assumption that they took the maximum of 30 supplements during the postpartum period, these women consumed at least 90 supplements during pregnancy. This finding compares

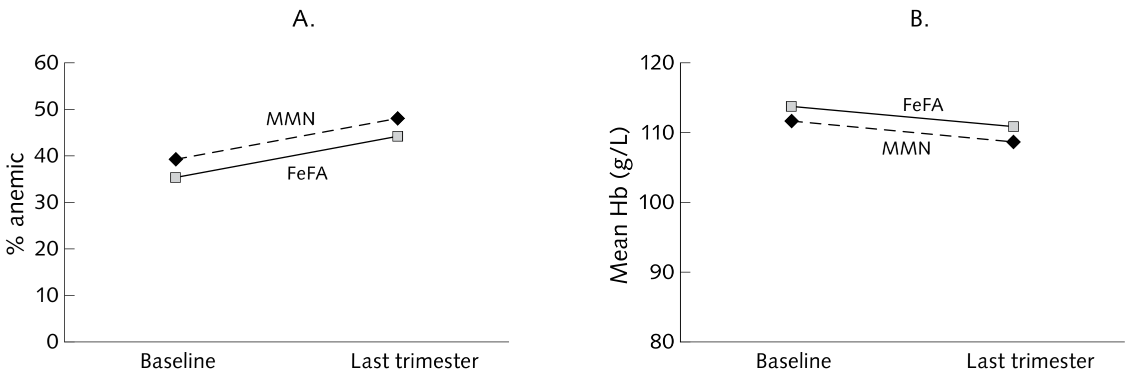

FIG. 2. Comparison of (A) percentage of women with anemia (hemoglobin < 110 g/L) and (B) mean hemoglobin levels at baseline and last trimester in groups receiving multiple micronutrients (MMN) and iron–folic acid (FeFA)

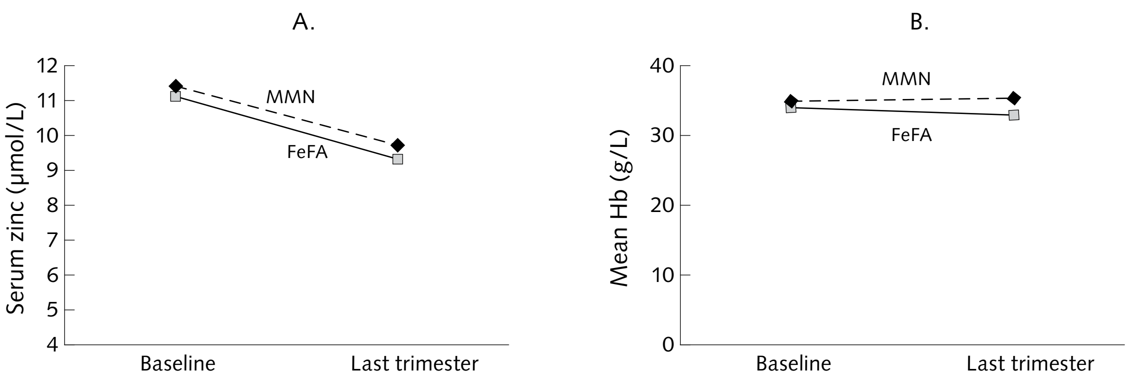

FIG. 3. Comparison of (A) mean serum zinc levels and (B) mean serum retinol levels at baseline and last trimester in groups receiving multiple micronutrients (MMN) and iron–folic acid (FeFA)

with only 29% of women who consumed at least 90 supplements during pregnancy as reported in the most recent Indonesia Demographic and Health Survey [19]. In the effectiveness study conducted in parallel with this study, in which supplements were delivered once a month, the mean number of supplements consumed was less, at 107 [20].

The mean adherence (defined as the percentage of days since enrollment on which women could take supplements during which supplements were actually taken) was about 70% in both groups. This means that on average women consumed the supplements on 5 of 7 days. No difference in adherence rates was seen between the two groups. However, even with active recruitment of pregnant women within the community, less than 10% of women started supplementation in the first trimester. Ensuring that women have access to supplements means that they will consume them, but starting supplementation during pregnancy is difficult even in a research study such as this. Reaching women before pregnancy may be necessary in order to improve micronutrient status before the second trimester.

Multivitamin supplementation was associated with a lower prevalence of LBW (6.3% in the group receiving multiple micronutrients vs. 7.3% in the iron–folic acid group). The sample size calculations predicted a 50% reduction in the rate of LBW, from 10% to 5%. The rate of LBW in our population was lower than that found in other Indonesian studies [15, 16], and the number of infants for whom birthweight data were available (384 in the group receiving multiple micronutrients and 341 in the iron–folic acid group) in this study was smaller than the number needed to account for the additional 20% cluster design effect (342 × 1.2 = 410). Therefore, the calculated sample size was inadequate to detect significant differences. In the absence of a placebo control, this study could not detect whether there was a net benefit of both antenatal supplements in reducing the rate of LBW over no supplementation whatsoever. Whether this difference of 14% or the mean birthweight difference of 40 g is programmatically relevant is controversial [21, 22].

Among women receiving multiple micronutrient supplements, only serum retinol levels increased significantly between baseline and the third trimester, resulting in a significant difference between the group receiving multiple micronutrients and the control group ($p < .01$). Although hemoglobin and ferritin levels during the last trimester were higher among women receiving iron–folic acid than among those receiving multiple micronutrient supplements, the iron–folic acid group had significantly higher levels at baseline. Despite the fact that both the intervention and the control supplements contained iron, neither supplement was able to fully compensate for the hemodilution occurring during pregnancy and prevent the decline in iron status between baseline and the last trimester. Surprisingly, zinc status did not improve with the use of multiple micronutrients, but improvement in zinc status may be related to measurement issues.

Although the study was not powered to detect the impact of multiple micronutrient supplementation on fetal loss and neonatal death compared with iron–folic acid, we observed a decrease in the combined outcome of fetal loss or neonatal death among women consuming 90 or more supplements.

Conclusions

This efficacy trial showed that multiple micronutrient supplements and iron–folic acid can be successfully distributed to pregnant women. When distribution is successful and women are supported to take supplements, adherence is not a problem. The slight increase in mean birthweight and the decrease in the rate of LBW, even though not significant, are consistent with the results of other studies reported in this journal supplement. The benefit of multiple micronutrient use on reduction of pregnancy loss is intriguing as well. Even though the amount of iron in the multiple micronutrient supplement was half that in the iron–folic acid supplement, no differences in anemia levels were noted between the two groups, a result suggesting that the inclusion of other nutrients in the multiple micronutrients is beneficial in addressing anemia.

Acknowledgments

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A comparative evaluation of multiple micronutrient and iron–folic acid supplementation during pregnancy in Pakistan: Impact on pregnancy outcomes

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Abstract

Background. *Maternal micronutrient deficiencies are widespread in Pakistan and are potentially associated with maternal undernutrition and intrauterine growth retardation. Intervention strategies largely consist of administration of iron–folic acid supplements during pregnancy.*

Objective. *We evaluated the acceptability of multiple micronutrient supplementation and its potential benefits on pregnancy outcomes and maternal micronutrient status in a cohort of pregnant women in rural and urban Sindh through a cluster-randomized design.*

Methods. *We randomly assigned 2,378 pregnant women to receive either iron–folic acid or multiple micronutrient supplements. The supplements were administered fortnightly by community health workers who performed home visits to assess tolerance and observe the mothers.*

Results. *The women in both groups consumed about 75% of the supplements provided, and few reported adverse effects such as vomiting, abdominal pain, etc. There was a small (70 g) but significant increase in birthweight among infants of mothers receiving multiple micronutrients as compared with infants of mothers receiving iron–folic acid supplements (2.95 ± 0.6 vs. 2.88 ± 0.5 kg, p = .01). This translated into a 10% reduction (p < 0.17) in the proportion of low-birthweight infants among infants of mothers receiving multiple micronutrients. Although stillbirth rates were comparable in the two groups, the early neonatal mortality rate in the group receiving multiple micronutrients was higher, although not significantly, than that in the group receiving iron–folic acid (43.2 vs. 23.5 deaths per 1,000 live births; RR = 1.64; 95% CI, 0.94 to 2.87). Comparable reductions in anemia (hemoglobin < 11 g/dL) were observed, although the proportion with low iron stores (assessed by serum ferritin) was lower in the iron–folic acid group in the postnatal period. Although the proportion of women with subclinical vitamin A deficiency after supplementation did not differ between the two groups, the iron–folic acid group had a higher proportion with lower serum zinc levels in the immediate postpartum period.*

Conclusions. *These data suggest that multiple micronutrient supplements are well tolerated during pregnancy, but the effect on birthweight is modest. The observed effect on early neonatal mortality suggests the need for further studies and careful assessment of the intervention in health system settings.*

Key words: Birthweight, iron–folic acid supplementation, multiple micronutrient supplementation, neonatal death, pregnancy, stillbirth

Background

Maternal undernutrition is widely recognized as a major public health issue in the developing world, and it is estimated that between 10% and 19% of women in many countries of the developing world are undernourished, with a body mass index (BMI) of less than 18.5 [1]. In addition to overt maternal undernutrition and short stature, micronutrient deficiencies are widespread and play a major role in increasing maternal morbidity and mortality [2]. It is estimated that iron deficiency contributes to an excess 115,000 maternal deaths and 0.4% of global total disability-adjusted life years (DALYs) lost [1]. Given widespread iron deficiency and the need for extra folic acid during pregnancy, maternal iron–folic acid supplementation has become the standard component of packages of antenatal care [3, 4]. However, there are issues with bioavailability and tolerance of various iron preparations [5], and in general the compliance within large-scale programs is poor [6]. There are additional concerns that iron–folic

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acid supplementation alone may not be sufficient to replenish deficiencies of other micronutrients in areas of endemic deficiencies. Based on these concerns, a multiple micronutrient supplement was developed for trial purposes by the World Health Organization (WHO), UNICEF, and the United Nations University (UNU) in 1999, which included a lower dose of iron and several additional micronutrients and aimed to provide a daily nutrient allowance [7] suitable for use in pregnancy.

It is recognized that maternal undernutrition, especially low BMI, significantly increases the risk of intrauterine growth retardation (IUGR) [1]. This may be associated with high rates of delivering a small baby, frequently recorded as low-birthweight (LBW) infants at birth (weighing < 2.5 kg). Such infants may represent a mixed group of preterm infants delivered before 37 weeks of gestation or, more commonly, term infants with IUGR. The latter may be associated with maternal undernutrition and, in particular, has been the focus of attention in nutrition interventions such as balanced energy–protein supplements [8] and multiple micronutrients [9].

We undertook a cluster-randomized, controlled trial to evaluate the efficacy and acceptability of the UNICEF maternal multiple micronutrient supplement in community settings in urban and rural Sindh (Pakistan) and its impact on maternal health and birth outcomes. The trial was approved by the Ethics Review Committee of the Aga Khan University.

Methods

Site selection and study design

We identified an urban population (Bilal Colony, Karachi) and rural villages (Kot Diji district, rural Sindh) as study populations on the basis of socioeconomic indicators and available health systems support. These areas were selected because the population mix and housing characteristics were similar to those seen in urban centers and agrarian populations in rural Pakistan. A previous pilot survey had indicated high rates of maternal undernutrition (15% with BMI < 18.5) and iron-deficiency anemia (65%) and a prevalence of LBW ranging from 18% to 40% [10].

A comprehensive baseline household census was undertaken to identify women of reproductive age and obtain information on family size, household characteristics, assets, dietary patterns, and pregnancy history. Women of reproductive age were provided information on the study design and the nature of the iron–folic acid or multiple micronutrient supplement and were invited to participate in the study if they became pregnant. The multiple micronutrient was the United Nations International Multiple Micronutrient Preparation (UNIMMAP) formulation [7] designed to provide 100% of the recommended dietary allowance of key vitamins and minerals, containing 30 mg of iron (ferrous fumarate) and 400 μg of folic acid along with 800 μg of retinol (retinyl acetate), 200 IU of vitamin D (ergocalciferol), 10 mg of vitamin E (α-tocopherol acetate), 70 mg of ascorbic acid, 1.4 mg of vitamin B_1 (thiamine mononitrate), 18 mg of niacin (niacinanide) 1.4 mg of vitamin B_2, 1.9 mg of vitamin B_6 (pyridoxine), 2.6 μg of vitamin B_{12} (cyanocobalamin), 15 mg of zinc (zinc gluconate), 2 mg of copper, 65 μg of selenium, and 150 μg of iodine. The control group received only iron (60 mg) and folic acid (400 μg), the standard of care within the programs of the Ministry of Health in Pakistan. The multiple micronutrient and the iron–folic acid tablets were identical in color, shape, and packaging and were manufactured by Danish Pharmaceutical Industries (Ballerup, Denmark).

The iron–folic acid and multiple micronutrient supplements were distributed by trained female community health workers who identified all pregnancies in their catchment populations through home visits. We randomly allocated the entire population of the urban and rural areas (population, 110,000; 20,400 households) into 28 discrete clusters (16 rural and 12 urban) on the basis of household characteristics, socioeconomic criteria, and geographic location. Each cluster was allocated to a community health worker who covered an average of 600 to 700 households with a population of 3,500 to 4,000. The community health workers received special training in field procedures and were trained to perform fortnightly household visits. They identified women of reproductive age, newlywed women, and suspected pregnancies within the first trimester. The community health workers developed close contacts and liaison with the local government health workers (lady health workers) and traditional birth attendants in their respective areas. Two research medical officers supervised seven clusters each and were assisted by a social scientist and fieldwork supervisor who supervised the data collection process.

Field procedures for intervention implementation and data collection

Two methods of community outreach were implemented. In one, the supplements were provided along with basic nutritional and antenatal care messages (focusing on the importance of maternal nutrition, antenatal care, and micronutrient supplements to avert maternal anemia) through home visits. The messages and counseling were in accordance with the curriculum and materials of the national program for family planning and primary health care [11]. In the other, the home visits were complemented with additional quarterly community-based group sessions held in the houses of community participants who volunteered the use of their households for such sessions. These group meetings were conducted by the community health workers and facilitated by a social scientist with training in nutrition and relied on a combination of static materials (counseling cards) and a docudrama specifically developed to emphasize the core messages.

For all women who were suspected to be pregnant, a written informed consent was obtained after explanation of the project objectives and procedures, and they were invited to participate in the screening examination and ultrasound confirmation of pregnancy. In both the urban and the rural populations, a trained obstetric ultrasonographer performed an examination of all eligible women who agreed to the examination within 7 days of identification of a suspected pregnancy to confirm and date the pregnancy. Those who did not have a confirmed pregnancy on ultrasound scanning or who were clearly advanced beyond 24 weeks of gestation were excluded from participation in the study. Those with a confirmed pregnancy at less than 16 weeks of gestation were invited to participate in the trial and allocated to either the iron–folic acid or the multiple micronutrient supplement according to their respective location and a block randomization code in groups of 20 maintained by the Aga Khan University pharmacy.

In order to minimize the risk of contamination, a cluster-based allocation strategy of supplements (either iron–folic acid or multiple micronutrients) by the community health workers was implemented. The allocation of either iron–folic acid or multiple micronutrient supplements and the distribution of the sealed, coded supplement bottles were independently controlled by the pharmacy at Aga Khan University, which maintained the allocation codes by individual community health workers. The pharmacy maintained a computerized database for the supply of supplements by respective community health workers, cluster allocation and respective block-randmization codes for pregnant women. All pregnant women were allocated a unique code and a uniquely labeled and numerically coded specific supplement supply for the duration of pregnancy, for storage in the field office. The field staff (medical officers, community health workers, social scientists, and data collection team) remained completely blinded as to the supplement allocation. The community health workers provided a fortnight's supply of supplements (multiple micronutrients or iron–folic acid) to the participants and performed a tablet count and stock replenishment at every fortnightly visit.

Clinical, anthropometric, and laboratory investigations

A medical officer performed a physical examination of all recruits at baseline after confirmation of pregnancy and treatment allocation. A 10-mL blood sample was obtained to assess maternal hemoglobin level as well as serum ferritin [12], zinc [13], and vitamin A [14]. At each fortnightly visit, the community health workers performed the maternal physical and clinical examination, including a morbidity assessment and measurement of fundal height. If problems were identified, referral was made to the local public sector referral facility for further care. Additional anthropometric measurements (height, weight, and mid-upper-arm circumference) were recorded with the use of standard measures and equipment (Seca Stadiometers and UNICEF Uniscales with a precision of 100 g). In case of any clinical problem, referral was made to the local public sector hospital for further medical assistance.

Evaluation of pregnancy outcomes and newborn assessment and follow-up

In addition to the fortnightly follow-up, the community health workers worked in close liaison with lady health workers and traditional birth attendants in their areas to identify each birth among participating women (in facilities or domiciliary settings). The newborn infants were weighed within 72 hours of birth with infant weighing scales (Tanita, Japan), and an additional assessment for gestational age [15] and well-being was also performed by the research medical officers. Additional newborn examinations assessing outcomes were performed by community health workers on the 7th, 14th, and 28th day of life. A maternal blood sample was also collected at the first postnatal visit for estimation of hemoglobin, serum ferritin, zinc, and vitamin A. We obtained information on birth outcomes as well as time of death until the end of the neonatal period (survival and deaths). In the absence of postmortem information, we obtained information on the cause of neonatal deaths through verbal autopsies conducted with the use of standardized instruments [16] and specifically trained medical officers. Allocation of the cause of death was done by a computer algorithm modified from standard algorithms [17] and previously applied to neonatal deaths in rural Sindh [18]. A hierarchical model was used for allocation of the cause of death, with extreme prematurity and birth asphyxia preceding diagnoses related to acquired problems such as infections [17].

Sample size estimation and analytical plan

We estimated the potential sample size needed for the study by two methods. Given the estimated birthweight of 2,600 g (pooled SD of 700 g) and a potential 5% gain in birthweight with the multiple micronutrients, we anticipated that 600 births would be needed in each group (taking into account dropouts and measurement losses) [19]. Given the planned implementation of the supplementation schedule by 28 possible clusters in the area (average cluster size of 100 pregnant women, intercluster correlation of 0.02, and design effect of 2), we estimated that a total of 920 subjects would be needed in each group (iron–folic acid or multiple micronutrients) to estimate a difference in birthweight of 150 g between the two groups with 90% power [20].

Apart from the ethnic mix of the population, no significant differences were found between the urban and rural populations for a range of characteristics, including a composite index of socioeconomic status (**table 1**). No differences were noted in the educational status or overall ethnic composition of the populations randomly allocated to the two nutrition intervention strategies. The results of the nutrition education intervention alone will be reported elsewhere, and this report will focus on the findings of the supplementation with the micronutrients.

TABLE 1. Maternal characteristics at admission according to urban or rural residence[a]

Characteristic	Urban (n = 967)	Rural (n = 1,411)
Age (yr)	25.3 ± 5.2	25.9 ± 5.3
BMI (kg/m^2)	22.8 ± 4.7	20.4 ± 3.3
Gravidity	4.1 ± 2.7	4.7 ± 3.3
Parity	2.7 ± 2.4	3.1 ± 2.8
SES quintile (%)		
1	15.2	12.1
2	10.8	6.6
3	18.2	42.0
4	22.6	16.4
5	33.2	14.0
Mean SES score[b]	3.6 ± 1.0	3.2 ± 0.97
Previous perinatal death (%)	9.7	12.8
History of problems reported at recruitment (%)[c]		
Severe vomiting	39.6	24.7
Headache	23.1	26.9
Fever	12.7	19.3
Vaginal discharge	2.4	0.9
Low blood pressure	11.3	0.3
Swelling of hands and feet	2.0	1.4

BMI, body mass index; SES, socioeconomic status.

a. Plus–minus values are means ± SD.

b. The composite SES score was estimated by assigning scores to individual SES variables as follows: Water supply: 1 for individual tap; 0.5 for community tap, hand pump or tube well; 0 for tanker, well, river or canal, or other. Toilet facilities: 1 for flush WC; 0.5 for non-flushing WC; 0 for waste carried away by sweeper, pit hole, community latrine, other. Lighting source: 1 for electricity; 0 otherwise. Housing construction: 1 for brick; 0.5 for mixed brick and mud or other materials; 0 for mud. Ownership: 1 for own house; 0 otherwise. Cooking fuel: 1 for piped or compressed natural gas; 0.5 for kerosene; 0 for wood, coal, manure, or other. Livestock ownership: 1 for any owned; 0 otherwise. Other assets: averaged over the following items owned and verified: air conditioner, television, washing machine, sewing machine, radio, cable television, and mobile phone. The asset score was derived as a proportion out of 7. Mode of transportation used by head of household: 0 for none; 0.5 for own motor bike; 0.75 for own car; 1 for own both forms of transport. Education of head of household: 0 for no formal schooling; 0.25 for primary schooling; 0.75 for secondary schooling; 1 for higher than secondary schooling.

c. Percentages do not add up to 100% because of multiple responses.

Results

Of a possible 2,964 pregnant women identified by the community health workers during pregnancy surveillance, 325 refused to participate in the study and the initial screening process. In all, 2,699 women were eligible for potential recruitment, of whom 1,185 were resident in the urban site (Bilal Colony) and 1,514 in the rural site (Kot Diji). The total refusal rate was 11% among these women, and an additional 261 women were excluded because the pregnancy could not be verified on ultrasound (136 women) or the pregnancy was advanced beyond the second trimester (55 women), or they moved away from the study area (70 women). **Figure 1** shows the CONSORT diagram for the study cohort.

In all, 2,378 women were randomized to either iron–folic acid or multiple micronutrient therapy. **Table 2** reports the baseline characteristics of the two intervention groups, indicating that there were no significant differences between the two groups for a number of pregnancy indicators and for micronutrient status. The baseline rates of anemia (hemoglobin < 11 g/dL) were comparable in the iron–folic acid and the multiple micronutrient groups (48.6% for iron–folic acid and 50% for multiple micronutrients, p = NS), and a similar number of mothers had evidence of low iron stores

TABLE 2. Maternal characteristics at admission[a]

Characteristic	Iron–folic acid) (n = 1,230)	Multiple micronutrients (n = 1,148)
Age (yr)	26 ± 5	26 ± 5
Gravidity	4.5 ± 3.1	4.4 ± 3.0
Parity	3.0 ± 2.7	2.9 ± 2.6
Weight (kg)	51.1 ± 10.1	50.4 ± 10.1
Height (cm)	153.3 ± 5.9	153.2 ± 6.0
MUAC (cm)	23.3 ± 3.3	23.3 ± 3.3
Body mass index (kg/m^2)	21 ± 4	21 ± 4
Hemoglobin (g/dL)	10.8 ± 1.5	10.7 ± 1.6
Ferritin (ng/mL)	29.3 ± 26.2	27.1 ± 27.3
Zinc (μg/dL)	65.7 ± 21.4	64.6 ± 21.6
Serum retinol (μg/dL)	39.6 ± 18.7	38.0 ± 17.4
Gestational age at recruitment (wk)[b]	12.2 ± 3.1	12.2 ± 3.0

BMI, body mass index; MUAC, mid-upper-arm circumference

a. Values are means ± SD.

b. Gestational age was determined by maternal last menstrual period and ultrasound scan dating.

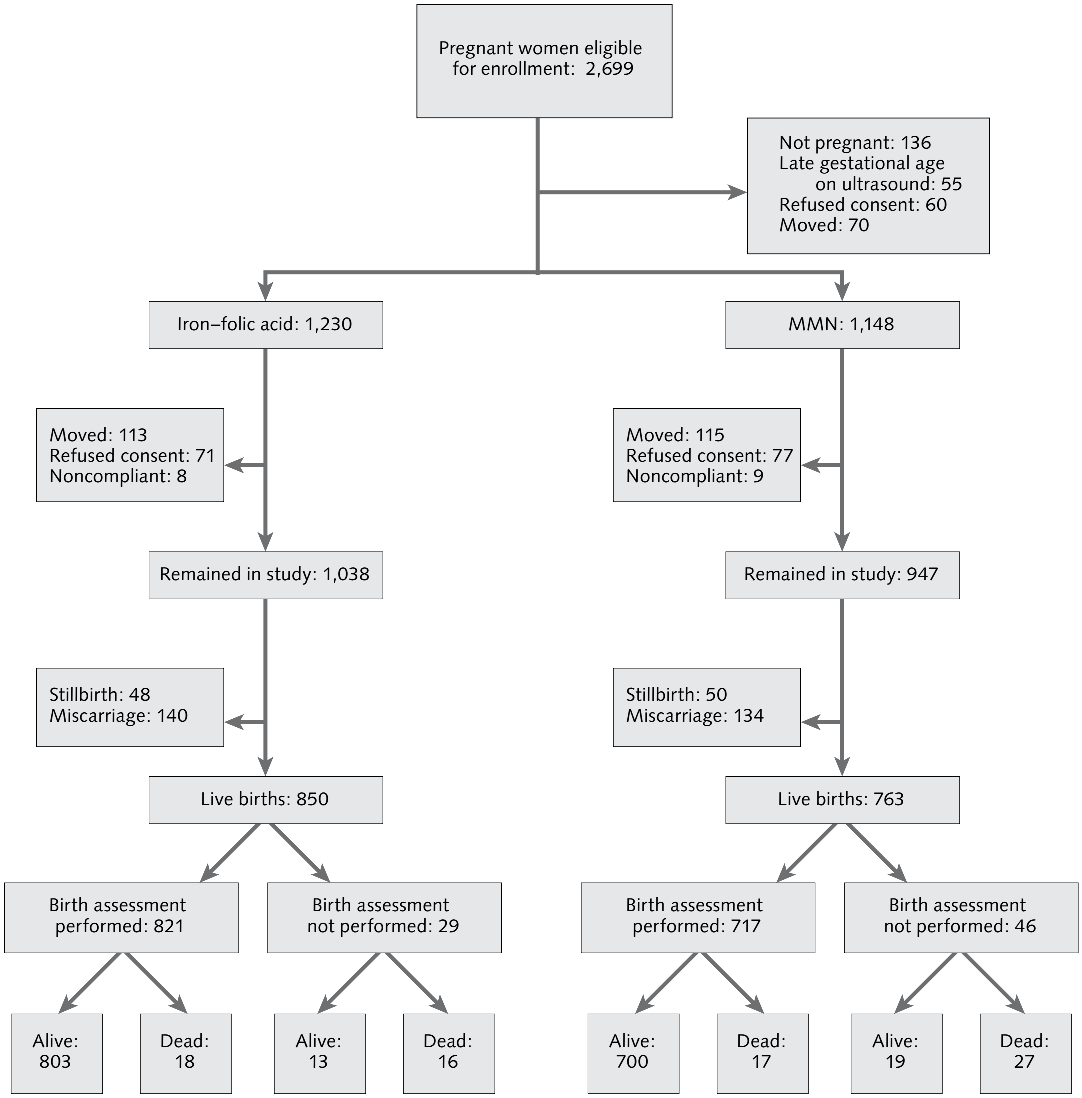

FIG. 1. CONSORT diagram of the study. MMN, multiple micronutrients

(serum ferritin < 12 ng/mL) at recruitment (32.4% for iron–folic acid and 38.7% for multiple micronutrients, p = NS). The two groups also had comparable rates of subclinical zinc deficiency (< 60 µg/dL) (44.3% for iron–folic acid and 45.2% for multiple micronutrients, p = NS) as well as subclinical vitamin A deficiency (serum retinol < 0.7 µmol/L) (10.7% for iron–folic acid and 10.9% for multiple micronutrients, p = NS).

Table 3 indicates the overall morbidity patterns during the current pregnancy, patterns of supplement consumption, and reasons for noncompliance, as reported for the two groups. The two groups had comparable rates of overall consumption of supplements and of various self-reported morbidities during the course of the follow-up.

Table 4 reports overall weight gain during pregnancy as well as anthropometric outcomes of the newborn infants. There was a small but significant increase of 70 g in birthweight among infants of mothers who had received multiple micronutrients in comparison with those whose mothers had received iron–folic acid supplements. This translated into a 10% reduction in the proportion of LBW infants (from 19.6% to 17.7%) among infants whose mothers received multiple micronutrient supplements. No differences were found between the two groups in mean gestational age at birth or in the rate of prematurity (28.3% for iron–folic acid and 28.7% for multiple micronutrients, p = NS).

Table 5 shows the impact of supplements on maternal micronutrient status in the 988 women for whom paired blood samples were available. The corresponding impacts on the proportion of women with anemia,

TABLE 3. Maternal morbidity and consumption of supplements during current pregnancy

Variable	Iron–folic acid (n = 1,206)	Multiple micronutrients (n = 1,134)
No. of antenatal care visits	9 ± 5	9 ± 5
Proportion of tablets consumed (%)	76.7	75.6
Reason for not taking supplements (%)[b]		
Forgot	6.3	8.6
Vomiting	4.6	5.6
Fear of side effects	2.3	2.2
Miscellaneous	5.6	6.3
Unclear	4.7	3.8
Morbidity		
Febrile episodes		
% of women	21.8	23.6
Episodes/mo	0.29 ± 0.2	0.35 ± 0.3
Backache		
% of women	36.1	39.2
Episodes/mo	0.7 ± 0.6	0.6 ± 0.5
Vomiting		
% of women	18.7	17.3
Episodes/mo	0.4 ± 0.5	0.3 ± 0.2
Cough		
% of women	21.5	16.5
Episodes/mo	0.4 ± 0.3	0.4 ± 0.3
General weakness		
% of women	27.8	26.9
Episodes/mo	0.4 ± 0.3	0.4 ± 0.2
Abdominal pain		
% of women	17.4	15.2
Episodes/mo	0.4 ± 0.4	0.3 ± 0.2
Edema		
% of women	17.3	16.6
Episodes/mo	0.5 ± 0.4	0.4 ± 0.3
Headache		
% of women	32.2	32.4
Episodes/mo	0.5 ± 0.5	0.4 ± 0.3

a. Plus–minus values are means ± SD. All differences are nonsignificant (p > .05).
b. Percentages represent most frequently reported responses from individuals in multiple follow-up visits.

low serum ferritin, and subclinical zinc and vitamin A deficiency are shown in **figure 2**. Overall, the improvement in the rate of anemia (hemoglobin < 11 g/dL) was comparable in the two groups; the anemia rates were 48.9% at initiation and 40.6% postnatally in the iron–folic acid group, and 50% at initiation and 44.2% postnatally in the group receiving multiple micronutrients. Although the proportion with low iron stores (as assessed by serum ferritin) was lower in the iron–folic acid group in the postnatal period for iron–folic acid 33% at initiation and 17.9% postnatal; the reduction in the proportion among women receiving multiple micronutrients 44.1% at initiation and 25.2% postnatal, was comparable). The proportion of women with subclinical vitamin A deficiency was also comparable between the two groups at the beginning and end of supplementation: the iron–folic acid group had a higher proportion with lower serum zinc levels in the immediate postpartum period.

Table 6 shows the data on stillbirths and neonatal deaths in the two groups. The rate of stillbirths in both groups was comparable (53.5/1,000 total births for iron–folic acid and 61.5/1,000 for multiple micronutrients; RR = 0.87; 95% CI, 0.59 to 1.28). The early neonatal mortality rate was higher in the group supplemented with multiple micronutrients than in the iron–folic acid group (43.2 vs. 23.5 deaths per 1,000 live births, respectively; RR = 1.64; 95% CI, 0.94 to 2.87), although the difference did not reach significance. The late neonatal mortality rates were comparable in the two groups (16.5/1,000 live births for iron–folic acid vs. 14.4/1,000 live births for multiple micronutrients; RR = 0.8; 95% CI, 0.4 to 1.9). **Table 7** details the cases of neonatal deaths as determined by verbal autopsies. No significant difference was noted in any of the main causes of neonatal deaths, and a number of early neonatal deaths were classified as of indeterminate cause.

In general, birthweights were higher (3.00 ± 0.50 vs. 2.86 ± 0.50 kg, p < .001) and the prevalence of LBW was lower (19.2% vs. 25.1%, p = .01) among infants of urban women than among infants of rural women. However, no differences were seen in the rates of stillbirth or neonatal mortality between urban and rural populations.

Discussion

Our study indicated that the iron–folic acid and multiple micronutrient supplements were well accepted and tolerated, with minimal reported gastrointestinal side effects. The intake of multiple micronutrient supplements was associated with better weight gain during pregnancy and a small (70 g) but significant increase in birthweight. The weight gain was not associated with an impact on duration of pregnancy or prematurity rates.

Notwithstanding the above, no significant improvement was noted in the iron status of women receiving multiple micronutrient supplements. In consonance with the findings that other micronutrients, such as riboflavin and vitamin A, could improve iron absorption [21, 22], the impact on hemoglobin concentration and anemia rate was comparable in both groups, even though those in the group receiving multiple micronutrients received half the amount of iron. Iron–folic acid supplements had a better impact on body stores, as indicated by ferritin estimation. In contrast, compared with those receiving multiple micronutrients, women receiving iron–folic acid had a higher prevalence of subclinical zinc deficiency, as estimated by serum zinc measurements.

The observed higher early neonatal mortality among infants of mothers receiving multiple micronutrient supplements was not apparently related to birth size, length of gestation, or care-seeking patterns and was equally distributed between the urban and rural arms of the study. The rates of difficult deliveries,

TABLE 4. Maternal weight gain and infants' anthropometric measurements at birth

Variable	Iron–folic acid (n = 1,230)	Multiple micronutrients (n = 1,148)	p
Maternal monthly weight gain (kg)	1.24 ± 0.8	1.38 ± 1.0	< .001
Maternal monthly gain in MUAC (cm)	0.18 ± 0.6	0.19 ± 0.6	.70
Infant birthweight (kg)	2.88 ± 0.5	2.95 ± 0.6	.01
Infant birth length (cm)	48.4 ± 2.8	48.3 ± 3.1	.46
Infant occipitofrontal circumference (cm)	33.4 ± 3.5	33.6 ± 3.1	.23
Infant MUAC (cm)	9.5 ± 1.3	9.6 ± 1.3	.50
Gestational age at birth (wk)			
Ultrasonographic	38.0 ± 4.0	38.0 ± 3.9	.71
Clinical assessment	36.8 ± 1.8	36.9 ± 1.6	.33
LBW (%)	19.6	17.7	.17

LBW, low birthweight; MUAC, mid-upper-arm circumference
a. Plus–minus values are means ± SD.
b. LBW is defined as < 2.5 kg.

TABLE 5. Biochemical indicators pre- and postsupplementation

Indicator	Iron–folic acid) (n = 522)		Multiple micronutrients (n = 466)		p^b
	Pre	Post	Pre	Post	
Hemoglobin (g/dL)	10.8 ± 1.5	10.9 ± 1.6	10.7± 1.6	10.9 ± 1.6	.27
Ferritin (ng/dL)	28 ± 24.4	48.9 ± 39.1	24.7 ± 26.9	40.0 ± 37.2	< .001
Zinc (μg/dL)	65.6 ± 20.9	59.9 ± 22.2	64.2 ± 20.2	67.1 ± 25.4	.004
Vitamin A (μg/dL)	38.0 ± 16.8	43.3 ± 21.4	37.7 ± 16.3	43.6 ± 25.8	.95

a. Values are means ± SD for paired observations.
b. The p values are for the comparison of postsupplementation values in the two treatment groups.

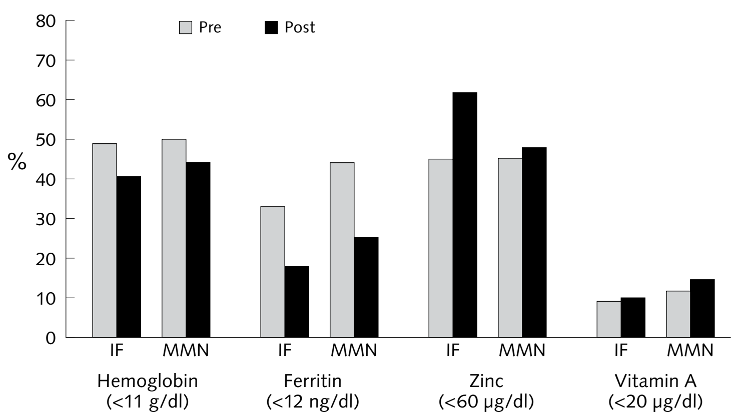

FIG. 2. Trends in prevalence of micronutrient deficiencies: proportions with anemia, low serum ferritin, and subclinical zinc and vitamin A deficiency (based on paired observations). IF, iron–folic acid; MMN, multiple micronutrients

instrumental births, and cesarean sections also did not differ between the two supplemented groups. A similar increase in newborn mortality has been observed with multiple micronutrient supplements in studies in Nepal [23, 24], but not in similar studies using comparable micronutrient preparations in Bangladesh [25] and Guinea-Bissau [26]. In contrast, a large study of multiple micronutrient supplementation during pregnancy in Indonesia was associated with significantly improved infant survival [27]. In contrast to the suggestion that the observed increase in neonatal mortality could be related to a shift in the birthweight distribution and potential increase in birth asphyxia [23], we could not find a comparable explanation for the excess early neonatal mortality in our study.

Notwithstanding the above, our study indicated that the lower dose of iron in the multiple micronutrient supplements was associated with an increase in maternal hemoglobin concentration and a reduction in the rate of anemia during pregnancy comparable to the effects associated with the standard-dose iron–folic acid preparation. Standard iron–folic acid preparations may be insufficient to address multiple micronutrient deficiencies during pregnancy in the developing world [28, 29], and alternative multiple micronutrient preparations that also address deficiencies of other micronutrients may be advantageous. Although we were not able to discern any significant difference in serum retinol concentrations among the multiple micronutrient supplemented women, the proportion of women with low serum zinc concentrations (< 70 µg/dL) after birth was greater among women receiving iron–folic acid supplements alone (61.8%) than those receiving multiple micronutrients (47.9%). The functional significance of these findings is unclear.

TABLE 6. Birth outcomes and timing of deaths

Variable	Iron–folic acid (*n* = 832)	Multiple micronutrients (*n* = 743)	*p*
Mode of delivery—%			.60
Normal	95.3	94.8	
Forceps	1.3	1.5	
Breech	0.6	1.3	
Cesarean section	2.7	2.4	
Stillbirths (≥ 28 wk)—no.	48	50	.47
Early neonatal deaths (≤ 7 days)—no.	20	33	.03
Late neonatal deaths (8–28 days)—no.	14	11	.74

TABLE 7. Classification of neonatal causes of death through computerized algorithm[a]

Cause of death	Iron–folic acid (*n* = 29)	Multiple micronutrients (*n* = 43)
Congenital abnormality	6 (20.7)	3 (7.0)
Prematurity	7 (24.1)	12 (27.9)
Birth asphyxia	12 (41.4)	11 (25.6)
Sepsis	1 (3.4)	3 (7.0)
Pneumonia	0	1 (2.3)
Could not be classified	3 (10.3)	13 (30.2)

a. Values are numbers (percent of total).

The findings that a multiple micronutrient preparation was associated with improved weight gain and birthweight have also been shown by others [23–26]. However, the benefits of a shift in birthweight distribution alone are uncertain and, in the absence of appropriate obstetric care and support, might potentially be associated with a higher risk of adverse pregnancy outcomes. It is therefore imperative that interventions to improve birthweight must be accompanied by comparable supportive strategies to improve maternal health and obstetric services. It is also likely that the benefits of improved maternal and fetal micronutrient interventions may accrue well beyond the immediate perinatal and neonatal period. Others have been able to demonstrate sustained benefits of maternal micronutrient interventions on infant survival [27] and on childhood growth [30] and developmental [25] outcomes. Given the demonstrated association of IUGR and maternal micronutrient deficiencies with long-term outcomes [31, 32], the benefits of multiple micronutrient supplementation in pregnancy may need to be measured well beyond birth outcomes and the neonatal period.

These findings underscore the need for large-scale evaluation of multiple micronutrient supplements during pregnancy in appropriate circumstances as part of health system interventions to improve maternal nutrition and health during pregnancy. It is also possible that the maximum gains of multiple micronutrient supplements may accrue if they are provided to adolescents and young women in the prepregnancy period [33, 34]. Our findings and those of others underscore the need for continued efforts to improve maternal nutrition among women of reproductive age and to consider the use of micronutrient supplements or fortification strategies in the context of the continuum of care for mothers, newborns, and children in undernourished populations [35].

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An effectiveness trial of multiple micronutrient supplementation during pregnancy in Vietnam: Impact on birthweight and on stunting in children at around 2 years of age

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Abstract

Background. *Multiple micronutrient deficiencies during pregnancy in Vietnam may contribute to poor fetal growth and stunting, which are major determinants of the health and development of future generations.*

Objective. *We assessed the effects of prenatal multiple micronutrient supplementation on maternal weight gain during pregnancy, infant birthweight, and height of the child at around 2 years of age.*

Methods. *We conducted a nonrandomized, non-blinded, side-by-side effectiveness trial in a normal program setting in three districts in the Red River Delta in the north of Vietnam. Women in one district received the standard iron–folic acid supplement during prenatal care; women in the second district received the multiple micronutrient supplement; in the third district, gender training was provided in addition to the multiple micronutrient supplement. Cluster surveys were carried out in the three districts at the end of the trial to verify low birthweight (LBW) and at around 2 years after the trial to measure children's height and weight, as well as to collect demographic data on the mothers.*

Results. *Mean birthweight was higher in the districts receiving multiple micronutrient supplements than in the district receiving iron–folic acid tablets. The mean birthweight was 166 g higher in the district receiving multiple micronutrients and 105 g higher in the district receiving multiple micronutrients with gender training than in the district receiving iron–folic acid ($p < .05$). The prevalence of LBW children (< 2,500 g) was lower in the district receiving multiple micronutrients (4.0%) and the district receiving multiple micronutrients plus gender training (5.8%) than in the district receiving iron–folic acid (10.6%) ($p < .05$). Children at around 2 years of age were taller in the district receiving multiple micronutrients (82.66 cm) and the district receiving multiple micronutrients plus gender training (83.61 cm) than in the district receiving iron–folic acid (81.64 cm), and the stunting rates were about 10% lower than in the district receiving iron-folic acid.*

Conclusions. *Multiple micronutrient supplementation during pregnancy could be an important intervention to help reduce stunting rates in Vietnam.*

Key words: Birthweight, multiple micronutrient supplements, pregnancy, stunting

Background

Vietnam has achieved remarkable progress in reducing the rate of underweight among children over the last few decades and is on track to achieve the Millennium Development Goal poverty target of halving the rate of child undernutrition by 2015 [1]. Despite such progress, however, almost a third of Vietnamese children are still stunted, and more worrying, the rate of stunting has stopped decreasing. Integrated nutrition programs for preschool children in Vietnam have been shown to improve complementary food intake [2], reduce morbidity [3], and reduce weight growth faltering during infancy among the most malnourished [4]. However, such programs seem to do little to prevent or cure moderate undernutrition, which is reflected more by stunting than by underweight per se.

In all countries with a child undernutrition problem, child growth faltering is confined to the first 2 years of life [5]. But whereas weight growth faltering occurs between 4 and 12 months of age, length growth faltering proceeds at a constant rate across the first 2 years of life, suggesting that weight growth faltering and length growth faltering are different processes. Furthermore, the early childhood length growth

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trajectory, or the potential for height growth, is largely set during gestation. In developed countries, the height of children under 5 years of age is greatly influenced by birthweight, with those with lower birthweights becoming the shorter children [6]. The magnitude of these differences is similar in both developed and developing countries, with those born with low birthweight (LBW) being about 5 cm shorter at 17 to 19 years of age [7]. Cole [8] has observed that the secular trend of increased adult height seen in most modern societies is largely explained by increases in the height achieved by children at 2 years of age. Both Cole and Karlberg [9] postulate that height gain in the first 2 years is the outcome of an interaction between concurrent nutrition and the growth rate set during pregnancy.

Most of the major factors associated with fetal growth retardation are nutrition related and include, among others, maternal height, prepregnancy weight, maternal birthweight, gestational weight gain, and gestational caloric intake [10]. In developing countries, the major factors associated with intrauterine growth retardation (IUGR) and/or LBW, besides race, are poor gestational nutrition, low prepregnancy weight, short maternal stature, and malaria. The estimated rate of LBW in Vietnam is 7% [11], with considerable variation across the country. A study of the maternal factors associated with LBW in northern Vietnam found rates of LBW varying from 7.9% to 12.5%, with higher rates in rural than in urban communities [12]. LBW was independently associated with maternal body mass index (BMI), food availability during pregnancy, maternity leave before delivery, and parity.

The development of a package of interventions to prevent LBW and protect fetal and infant growth has been promoted by UNICEF in various countries around the world, including Vietnam [13]. Part of the package of interventions is a multiple micronutrient supplement for use during pregnancy and lactation, the formulation of which has been agreed upon by the World Health Organization (WHO), UNICEF, and the United Nations University (UNU) for trial purposes [14]. Efficacy trials have been conducted in six countries, and a pooled data analysis of those studies has been agreed upon [15]. The results from other countries involved in these trials have already shown multiple micronutrient supplementation during pregnancy to have a favorable effect on birthweight [16–18] as well as on early child mortality [19].

The purpose of this study was to evaluate the effectiveness of multiple micronutrient supplementation as part of a package of interventions being delivered in a regular program setting, aimed at improving maternal nutrition during pregnancy, in order to improve birthweight and length growth of young children in the first 2 years of life in Vietnam. The effects of the multiple micronutrient supplements were compared with those of the standard iron–folic acid supplements that are routinely provided to mothers during pregnancy in most parts of Vietnam.

Methods

Study setting

The trial was carried out in three districts near Hanoi in the north of Vietnam. The three districts were Kim Son, with a population of 175,000, in Ninh Binh Province; Binh Luc, with a population of 155,000, in Ha Nam Province; and Vinh Bao, with a population of 185,500, in Thai Binh Province. All three districts were essentially rural, with the majority of families involved in farming, and especially rice production, in this fertile Red River Delta region.

Study design and interventions

This effectiveness trial comparing iron–folic acid supplementation with multiple micronutrient supplementation during pregnancy was run "side-by-side" in a normal program setting in the three districts, covering most pregnancies occurring in the years 2001 and 2002. In all three districts, UNICEF was providing support to the Ministry of Health to improve the capacity of district and commune health services in planning, implementing, and monitoring their activities, particularly antenatal care and safe delivery practices, with the active participation of communities (community-based monitoring approach). This support aimed to strengthen reproductive and maternal health services to enable them to provide adequate antenatal care, postnatal care, and safe delivery practices, as well as to increase pregnant women's access to and utilization of the same. In all three districts, mothers were actively sought out in early pregnancy by the village health workers and encouraged to come early to the antenatal clinic.

The study was approved by the ethical committee of the National Institute of Nutrition before implementation. Written informed consent was obtained from all pregnant women participating in the study and from their husbands. Participation was voluntary, and participants had the right to refuse enrollment in the study. Participants were given a health and nutrition consultation after the study was completed, and were provided with their test results.The identity of the participants was kept confidential and used only for research purposes.

The interventions delivered through antenatal care services in the three districts are summarized in **table 1**. In all districts, the village health workers were trained in aspects of nutrition during pregnancy so that they could encourage the mothers to eat more frequently during pregnancy. The multiple micronutrient

TABLE 1. Interventions delivered to pregnant women through mother and child health care services in the three districts

District	Intervention
Kim Son	Multiple micronutrients Nutrition education
Binh Luc	Multiple micronutrients Nutrition education Gender training
Vinh Bao	Iron–folic acid Nutrition education

TABLE 2. Composition of multiple micronutrient supplement for pregnant and lactating women (United Nations International Multiple Micronutrient Preparation [UNIMMAP]) recommended for trial purposes by UNICEF/United Nations University/World Health Organization

Nutrient	Amount
Vitamin A	800 μg
Vitamin D	200 IU
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B_1	1.4 mg
Vitamin B_2	1.4 mg
Niacin	18 mg
Vitamin B_6	1.9 mg
Vitamin B_{12}	2.6 μg
Folic acid	400 μg
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 μg
Iodine	150 μg

supplement was introduced for the duration of the trial in two districts (Kim Son and Binh Luc), and in the third (Vinh Bao) the regular iron–folic acid supplementation was maintained. In Binh Luc District, special training of the village health workers and health staff was also carried out on gender awareness aimed at improving maternal care by the family and community during pregnancy. The treatments were not blinded and there was no randomization of treatments. No true placebo control group could be used in the trial, since maternal anemia rates are high in Vietnam and the national policy and standard procedure is to provide iron–folic acid tablets to all mothers as part of prenatal care. In the "control" district of Vinh Bao, the Commune Health Station workers and the village health workers actively encouraged the mothers to have monthly antenatal visits. In the other two districts, women were encouraged to have at least three antenatal care visits during pregnancy.

The method of delivery of the antenatal care micronutrient supplements (both iron–folic acid and multiple micronutrients) was modified from usual practice in all three districts for the purpose and duration of the trial. Instead of the mother's receiving her supplements at the antenatal care on a monthly basis, the supplements were delivered to the mother's house by the village health worker on a weekly basis. The supplements were kept in the house in a special bottle. The village health worker asked to see the bottle each week, discussed with the mother whether the pills were being taken, and then replenished the bottle accordingly. The iron–folic acid supplements were those regularly provided by the Ministry of Health and contained 60 mg of iron and 400 μg of folic acid. The multiple micronutrient supplement (United Nations International Multiple Micronutrient Preparation [UNIMMAP]), which was provided by UNICEF through its supply division in Copenhagen, contained 15 vitamins and minerals, as shown in **table 2**.

Measurement methods and data collection

For the purpose of the study, various modifications were made to the routine measurement methods used in the care. The weighing of the baby soon after birth was greatly facilitated by the provision of a table beam balance baby-weighing scale (Seca model 725000) accurate to 10 g at each Commune Health Station. Since most mothers had their babies at the Commune Health Station, babies born in the study were usually weighed there at birth; if they were born elsewhere, they were weighed within 24 hours. The regular weighing of the mother during pregnancy was performed at each antenatal care contact with a Uniscale (Seca model 710). Although this monthly weighing was originally proposed to be performed at home by the village health worker, in most places it was performed at the Commune Health Station. In three communes of each district, all women were also given two blood tests to determine their anemia status during pregnancy, one during the first trimester of pregnancy and another before delivery. The tests were carried out by the HemoCue [20] method, and the results were entered in the mothers' records. The data, which were routinely collected by the commune health staff and the village health workers and noted in the Commune Health Center records, were collected for the years 2000 and 2001 for each of the three districts and were analyzed as a whole.

In addition to the routine data collection, two surveys were carried out by researchers from the National Institute of Nutrition, one at the end of the study in March 2003 and another 2 years later in March 2005. The 2003 survey focused on birthweight, and the 2005 survey focused on stunting in the 2-year-old children. For each survey, seven communes were randomly selected in each district. In each commune of these districts, mothers with children born between January 2002 and April 2003 were chosen as the subject of study, and their records in the Commune Health Station were compiled into a database. In the second survey, the children of these mothers were also weighed and measured with the use of Seca electronic weighing scales and UNICEF length instruments. Blood tests were performed by the HemoCue method. The two cluster samples were from different groups of children.

Statistical analysis

Statistical analysis was performed with the use of SPSS and Epi Info, version 6.04. Anthropometric indicators, including weight-for-age, height-for-age, and weight-for-height, were compared with National Center for Health Statistics (NCHS) reference data [21]; a cutoff point of −2 z-scores was used to classify the children according to their nutritional status. LBW was defined as less than 2,500 *g*. The *t*-test was used to compare the means, and the chi-square test was used to compare the percentages or prevalence rates of LBW, stunting in children, maternal weight gain during pregnancy, and anemia among mothers and children.

The sample size needed for both survey 1 and survey 2 was calculated by the formula $n = Z^2 \cdot p \cdot (1-p) - e^2$, where $Z = 1.96$, $e = 5\%$, $p = 14\%$ as the estimated rate of LBW in survey 1, and $p = 17\%$ as the estimated rate of stunting in survey 2. The selection procedure was corrected for two stages of sampling, whereby at least seven communes (one cluster) were randomly selected in each district, and 50 subjects were randomly selected in each commune cluster. The total numbers of subjects needed for each district, based on the above formula, were 320 for survey 1 on LBW and 200 for survey 2 on stunting. All twins were excluded from the statistical analysis.

Results

Routine monitoring system

As shown in **table 3**, some 12,000 births occurred in the three districts during the period of the supplementation trial (March 2000 to December 2001). The results from the routine monitoring system suggest that mothers in Kim Son (multiple micronutrients) had the best weight gain during pregnancy, with a far higher proportion of mothers gaining more than 9 kg during pregnancy. Kim Son also had the lowest rate of LBW. The worst weight gain during pregnancy was in Vinh Bao (iron–folic acid), where one-quarter of the mothers gained less than 6 kg during pregnancy. In the two districts that distributed multiple micronutrient supplements, no woman had a weight gain during pregnancy of less than 6 kg. The routine information system also showed that there was little or no significant difference in anemia rates across the three districts at the end of the trial, and in all three districts there was an improvement compared with the initial levels observed in early pregnancy at the first antenatal contact.

Data on the timing of initiation of supplementation and on compliance were not coded for analyses and thus are not available now. However, there was active surveillance of pregnant women in the community, and thus it is likely that supplementation started in the first trimester for a high proportion of women.

Population characteristics in sample surveys 1 and 2

As shown in **table 4**, the combined 2002 and 2004 sample surveys included a total of 1,579 mothers, with 517 from Vinh Bao District where iron–folic acid tablets were supplied during pregnancy, 527 from Kim Son District where multiple micronutrient tablets

TABLE 3. Overall results of the trial of multiple micronutrients in three districts from the Red River Delta region in 2000–01, based on data obtained from routine health system monitoring

Result	Kim Son (multiple micronutrients)	Binh Luc (multiple micronutrients plus gender training)	Vinh Bao (iron–folic acid)
No. of births	3,196	5,924	3,545
Low birthweight (%)	1.8	7.5	7.6
Weight gain during pregnancy (%)			
< 6 kg	0	0.1	23.1
6–9 kg	32.8	60.2	40.5
> 9 kg	67.2	39.7	36.4
Anemia prevalence (%)			
Initial (1st gestational trimester)	17.6	19	25
End (before delivery)	13.4	12.8	13.3

TABLE 4. Baseline characteristics of mothers before the intervention (surveys 1 and 2) — no. (%)

Characteristic	Binh Luc—multiple micronutrients plus gender training) (*n* = 535)	Kim Son—multiple micronutrients (*n* = 527)	Vinh Bao—iron–folic acid (*n* = 517)
Age (yr)			
< 19	0	0	7 (1.4)
19–35[a]	483 (90.3)	501 (95.1)	481 (93.0)
> 35	52 (9.7)	26 (4.9)	29 (5.6)
Occupation			
Farming[b]	509 (95.1)	453 (86.0)	451 (87.2)
Business	5 (0.9)	28 (5.3)	18 (3.5)
Government	21 (3.9)	46 (8.7)	48 (9.3)
Education			
Illiterate	2 (0.4)	2 (0.4)	4 (0.8)
Primary or intermediary	459 (85.8)	429 (81.4)	410 (79.3)
Secondary or higher[c]	74 (13.8)	96 (18.2)	103 (19.9)
Economic status [d]			
Rich	36 (6.7)	37 (7.0)	10 (1.9)
Normal	455 (85.0)	468 (88.8)	434 (83.9)
Poor[d]	44 (8.2)	22 (4.2)	73 (14.1)
Gravidity			
1	178 (33.3)	193 (36.6)	241 (46.6)
2	230 (43.0)	208 (39.5)	204 (39.5)
≥ 3[e]	127 (23.7)	126 (23.9)	72 (13.9)

a. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-squared test).
b. $p < .05$: Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-squared test).
c. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-squared test).
d. Poverty line Standard of General Statistics Office of Vietnam in 2004; Poor household is household below the poverty line Standard of General Statistics Office of Vietnam in 2004; Normal household is household above the poverty line Standard of General Statistics Office of Vietnam in 2004; $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-squared test).
e. $p < .05$: Binh Luc vs. Vinh Bao, Kim Son vs. Vinh Bao (chi-squared test).

were supplied during pregnancy, and 535 from Binh Luc District where multiple micronutrient tablets were supplied during pregnancy together with gender awareness training. On the basis of the demographic data collected from this sample of mothers from across the three districts, mothers from Kim Son (multiple micronutrients) tended to be a little older, were less likely to be farmers, and were more likely to have a better education than mothers from Vinh Bao (iron–folic acid), with mothers from Binh Luc (multiple micronutrients plus gender training) tending to be intermediate between the two.

Pregnancy and birth outcomes in sample surveys 1 and 2

According to the sample surveys, there were no significant prepregnancy differences among mothers in the three districts in mean height or weight or in the proportions of shorter or lighter mothers (**table 5**). Despite this similarity prior to the interventions, the mean weight gain during pregnancy was highest in Kim Son (multiple micronutrients) at 8.7 kg and lowest in Vinh Bao (iron–folic acid) at 7.6 kg ($p < .05$). The percentage of mothers in Vinh Bao with weight gain of less than 6 kg during pregnancy (26.1%) was almost three times higher than that in Kim Son (8.9%). Similarly, the percentage of mothers with weight gain of at least 9 kg during pregnancy was highest in Kim Son (54.6%) and lowest in Vinh Bao (31.3%) ($p < .01$).

Table 6 shows that the prevalence of anemia in the women was higher before intervention (during the first trimester of gestation) than at the end of intervention (just before delivery) and decreased most in Vinh Bao, where the standard iron–folic acid tablets were taken. The prevalence of anemia before intervention was highest in Vinh Bao (28.4%) and lowest in Kim Son (multiple micronutrients) (18.0%) ($p < .05$). The prevalence of anemia at the end of intervention was highest in Kim Son (10.0%) and lowest in Vinh Bao (7.4%) ($p > .05$). There was 21% reduction (from 28.4 before intervention to 7.4 % after intervention) of anemia

TABLE 5. Maternal weight and height before pregnancy and weight gain during pregnancy (surveys 1 and 2)

Variable	Binh Luc—multiple micronutrients plus gender training) (*n* = 535)	Kim Son—multiple micronutrients (*n* = 527)	Vinh Bao—iron–folic acid (*n* = 517)
Height before pregnancy			
Mean ± SD (cm)[a]	152.7 ± 4.7	153.8 ± 4.9	153.4 ± 4.6
Distribution — no. (%)[b]			
< 145 cm	17 (3.2)	16 (3.0)	14 (2.7)
≥ 145 cm	518 (96.8)	511 (97.0)	503 (97.3)
Weight before pregnancy			
Mean ± SD (kg)[c]	45.5 ± 4.3	45.3 ± 4.5	45.4 ± 4.2
Distribution — no. (%)[d]			
< 45 kg	215 (40.2)	224 (42.5)	229 (44.3)
≥ 45 kg	320 (59.8)	303 (57.5)	288 (55.7)
Weight gain during pregnancy			
Mean ± SD (kg)[e]	7.9 ± 2.3	8.7 ± 2.2	7.6 ± 2.4
Distribution — no. (%)			
< 6 kg[f]	91 (17.0)	47 (8.9)	135 (26.1)
≥ 6 < 9 kg	256 (47.9)	192 (36.4)	220 (42.6)
≥ 9 kg	188 (35.1)	288 (54.6)	162 (31.3)

a. $p > .05$ (*t*-test).
b. $p > .05$ (chi-squared test).
c. $p > .05$ (*t*-test).
d. $p > .05$ (chi-squared test).
e. $p < .05$: Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (*t*-test).
f. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-squared test).

TABLE 6. Prevalence of anemia during first gestational trimester and before delivery (surveys 1 and 2)

Variable	Binh Luc—multiple micronutrients plus gender training (*n* = 78)	Kim Son—multiple micronutrients (*n* = 211)	Vinh Bao—iron–folic acid (*n* = 148)
During 1st gestational trimester[a]			
Anemic	20 (25.6)	38 (18.0)	42 (28.4)
Normal	58 (74.4)	173 (82.0)	106 (71.6)
Before delivery[b]			
Anemic	7 (9.0)	21 (10.0)	11 (7.4)
Normal	71 (91.0)	190 (90.0)	137 (92.6)

a. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-square test).
b. $p < .05$: Binh Luc vs. Vinh Bao, Kim Son vs. Vinh Bao (chi-square test).

among pregnant women in Vinh Bao, a significantly greater reduction than that in Binh Luc (16.6%) and Kim Son (8.0%).

As shown in **table 7**, mean birthweight was significantly higher in the districts receiving multiple micronutrient supplements (Kim Son and Binh Luc) than in the district receiving iron–folic acid tablets (Vinh Bao). The mean birthweight was 166 g higher in Kim Son (multiple micronutrients) and 105 g higher in Binh Luc (multiple micronutrients plus gender training) than in Vinh Bao (iron–folic acid) ($p < .05$). The rate of LBW (< 2,500 g) was lowest in Kim Son (4.0%) and highest in Vinh Bao (10.6%) ($p < .05$), and the rate of high birthweight (≥ 3,500 g) was highest in Kim Son (22.6%) and lowest in Vinh Bao (10.3%) ($p < .05$).

Child undernutrition in sample survey 2

The results of the sample survey to collect child anthropometric data at around 2 years of age are shown in **table 8**. Children from Kim Son and Binh Luc, whose mothers had taken the multiple micronutrient supplement, were taller than children from Vinh Bao, whose mothers had taken iron–folic acid tablets. The

TABLE 7. Birthweight (surveys 1 and 2)

Variable	Binh Luc—multiple micronutrients plus gender training (*n* = 535)	Kim Son—multiple micronutrients (*n* = 527)	Vinh Bao—iron–folic acid (*n* = 517)
Mean ± SD birthweight (g)[a]	3,070 ± 428	3,131 ± 422	2,965 ± 404
Distribution of birthweight—no. (%)			
< 2,500 g[b]	31 (5.8)	21 (4.0)	55 (10.6)
2,500–2,999 g	162 (30.3)	131 (24.9)	205 (39.7)
3,000–3,499 g	241 (45.0)	256 (48.6)	204 (39.5)
≥ 3,500 g	101 (18.9)	119 (22.6)	53 (10.3)

a. $p < .05$: Binh Luc vs. Vinh Bao, Kim Son vs. Vinh Bao (*t*-test).
b. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao (chi-square test).

TABLE 8. Undernutrition in children around 2 years of age (survey 2)[a]

Indicator	Binh Luc—multiple micronutrients plus gender training (*n* = 172)	Kim Son—multiple micronutrients (*n* = 203)	Vinh Bao—iron–folic acid (*n* = 211)
Weight (kg)	10.57 ± 1.27	10.40 ± 1.10	10.07 ± 1.26
Height (cm)[b]	83.61 ± 3.96	82.66 ± 6.41	81.64 ± 3.96
WAZ	−1.67 ± 0.89	−1.61 ± 0.84	−1.77 ± 0.90
HAZ	−1.25 ± 0.98	−1.18 ± 1.04	−1.45 ± 1.04
WHZ	−1.08 ± 0.74	−1.10 ± 0.73	−1.17 ± 0.76
Stunting (%)[c]	20.9	20.7	29.4
Underweight (%)	35.5	33.0	43.6
Wasting (%)	9.9	8.9	11.8

HAZ, height-for-age z-score, WAZ, weight-for-age z-score, WHZ, weight-for-height z-score
a. Plus–minus values are means ± SD.
b. $p < .05$: Binh Luc vs. Vinh Bao, Binh Luc vs. Kim Son, Kim Son vs. Vinh Bao) (*t*-test).
c. $p < .05$: Binh Luc vs. Vinh Bao, Kim Son vs. Vinh Bao (chi-square test).

prevalence of stunting among children around 2 years of age was significantly less in the districts receiving multiple micronutrients (20.9% in Binh Luc and 20.7% in Kim Son) than in Vinh Bao (29.4%), where the mothers received iron–folic acid ($p < .05$). Despite the differences in stunting rates, there were no differences in mean weight or in the proportion of underweight children among the three districts.

Child anemia in sample survey 2

Table 9 shows that the prevalence of anemia in children around 2 years of age was twice as high in Vinh Bao (45.0%) as in Kim Son (21.2%), with Binh Luc in between (38.4%). The prevalence of anemia was higher in children under 2 years of age than in children 2 years of age or older.

Discussion

The results of the study suggest that prenatal supplementation with multiple micronutrients has a greater effect on birthweight than supplementation with iron–folic acid. The LBW rates in the districts where mothers were taking multiple micronutrients were half that in the district where mothers were taking iron–folic acid tablets. The mean birthweights of around 3 kg found in the three districts of the Red River Delta are similar to those reported in studies from Indonesia [19], Zimbabwe [18], and Niger [16], as compared with less than 3 kg in supplementation trials in Nepal [17] and India [22]. The differences in mean birthweight of 100 g (Binh Luc) and 150 g (Kim Son) in the districts receiving multiple micronutrients compared with the district receiving iron–folic acid are twice as large as those found in these other trials of multiple micronutrient supplementation during pregnancy and are similar to those achieved by giving mothers food supplements during pregnancy in the Gambia [23].

The differences in birthweight among the districts were unlikely to be due to differences in the condition of the mothers other than those introduced by the program interventions. Those factors most likely to influence birthweight, such as maternal height and prepregnancy weight, were essentially the same in all three districts. Although few women in the study were short (< 145 cm), a third were thin (< 45 kg). The mean

TABLE 9. Anemia in children around 2 years of age (survey 2)—no. (%)[a]

Age group	Number (percent)		
	Binh Luc—multiple micronutrients plus gender training (n = 172)	Kim Son—multiple micronutrients (n = 203)	Vinh Bao—iron–folic acid (n = 211)
< 2 yr[a]	14/31 (45.2)	24/76 (31.6)	52/107 (48.6)
≥ 2 yr[b]	52/141 (36.9)	19/127 (15.0)	43/104 (41.3)
Total[c]	66/172 (38.4)	43/203 (21.2)	95/211 (45.0)

Highlighted percentages were calculated based on total number of < 2 yr old children and > 2 yr old children of each district as above:

< 2 yr: children from 18 to < 24 months of age

> 2 yr: children from 24 to < 36 months of age

a. $p < .05$: Kim Son vs. Vinh Bao

b. $p < .05$: Binh Luc vs. Vinh Bao

c. $p < .001$: Kim Son vs. Vinh Bao, Kim Son vs. Binh Luc, t-test

weight and height of mothers before pregnancy were higher than those of women aged 18 to 25 years in the National Nutrition Survey in 1987–89 [24], suggesting that nutritional conditions in the three districts are somewhat better than the national average. A secular trend toward increased size at birth has been described in Hanoi, where the rate of LBW was just 5.1% in 1998 [25]. Interestingly, although birthweight was associated with maternal BMI before pregnancy and weight gain during pregnancy, it was not associated with maternal height in this study.

Weight gain during pregnancy was higher in the districts where mothers took multiple micronutrient supplements during pregnancy than in the district where mothers took iron–folic acid tablets, although the difference was significant for only one of the districts receiving multiple micronutrients (Kim Son). Weight gain during pregnancy was higher in all three study areas (7.9 kg in Binh Luc, 8.7 kg in Kim Son, and 7.6 kg in Vinh Bao) than the 6.6-kg gain found in Red River Delta areas in 1990 [26], but it was still less than the minimum of 12.7 kg recommended by the US Institute of Medicine for short women with low BMI [27].

Stunting rates in children around 2 years of age in the districts where mothers took multiple micronutrient supplementation during pregnancy were 10% lower than that in the district receiving iron–folic acid supplements**.** Very few studies have looked at postnatal growth of the children of mothers supplemented with food or micronutrients during pregnancy. One study in East Java, Indonesia, that provided mothers with either high- or low-energy supplements during pregnancy found a 100-g difference in mean birthweight between the two groups [28]. The longitudinal study on effect of energy supplementation during pregnancy and postnatal growth for the first 5 years of life in Madura, East Java showed that childen of mothers who received the high-energy supplement were taller throughout the first 5 years ($p < 0.005$ from 15 to 48 months, $p < 0.05$ at both 3–12 and 60 months) and stunting (height-for-age) was less prevalent than among children of mothers who had received the low-energy supplement, although there was no difference between the groups in the rate of underweight [29].

The reduction of anemia during the course of the study was greatest in the districts with the highest initial anemia rates. The greater improvement of anemia status in Vinh Bao may be due to the fact that the women were supplemented with 60 mg of elemental iron per day, as opposed to the 30 mg provided in the multiple micronutrient supplement in Kim Son. However, Binh Luc District also showed a similarly large reduction, even though mothers were taking only 30 mg of iron in the multiple micronutrient supplement. This suggests that the multiple micronutrient supplement is as effective as the iron–folic acid supplement for controlling anemia and that the more important factor was the initial level of the anemia.

It is well recognized that iron supplementation works as long as there is enough effort put into the delivery system [30]. When access to supplements is guaranteed and when they are provided with minimal, consistent, and easily understandable information and counseling, women adhere to prenatal and postpartum micronutrient supplementation [31]. Studies in Vietnam have shown that iron tablet distribution has a low priority among commune officials, although the recipients are keen to take the tablets. Ensuring availability and frequent supply of the tablets was the most critical factor for continued tablet taking [32]. The altered delivery system used in this project (mothers received the tablets in their homes together with encouragement to take the tablets), together with "active case seeking" (looking in the community for pregnant women early in pregnancy) probably meant that mothers were found earlier in pregnancy than before, when the mother had to go to the health center to get antenatal care.

Interestingly, despite the success of micronutrient supplementation during pregnancy at bringing down anemia rates in the mothers, the prevalence of anemia in children at 2 years of age was higher than the prevalence of anemia in their mothers prior to pregnancy, especially in those whose mothers received iron–folic acid supplementation during pregnancy. This suggests that the anemia is not just related to iron status per se and that other factors, such as gastrointestinal parasites, should be considered as possible causes.

With vitamin A deficiency, iodine-deficiency disorders, and iron-deficiency anemia affecting at least a third of all pregnant and lactating women and their children [33], the potential for micronutrient supplements to have a positive impact on maternal health as well as fetal and infant growth and development in Vietnam is potentially great. The extent of maternal zinc deficiency is not known for sure, but there is evidence that it exists in preschool children, since efficacy trials of zinc supplementation for growth-retarded children aged 4 to 36 months have had a positive impact on the growth of young children in Vietnam [34]. Furthermore, daily multiple micronutrient supplements containing zinc and iron performed better than iron supplements in improving hemoglobin status and length growth in young children [35].

We have no information on other factors likely to impact stunting, such as the promotion of exclusive breastfeeding, continued breastfeeding, and adequate complementary feeding in the study populations. Premature complementary feeding has been shown to be associated with poorer growth in the first 6 months of life, and predominant breastfeeding was associated with better length gain in the second semester of life among infants in Hanoi [36]. The rates of exclusive breastfeeding and adequate complementary feeding are far from optimal. If interventions to improve infant and young child feeding were put in place together with multiple micronutrient supplementation during pregnancy, it might be feasible to reduce the stunting rates in young children even more.

The addition of gender training did not seem to confer any extra benefit on birth outcomes. There were no differences in anemia rate, weight gain during pregnancy, birthweight, or the rate of young child stunting between Kim Son (multiple micronutrients) and Binh Luc (multiple micronutrients plus gender training), a result calling into question the effectiveness of the gender training given to the commune health workers and commune nutrition collaborators. Gender awareness training may have improved the knowledge of commune health and nutrition network staff, but it was not enough to bring about changes at the household level, such as a reduced workload for pregnant women or increased attention from men to the care and nutrition of pregnant women. Although the results of this study are not conclusive because the study populations were not randomized and the treatments were not blinded, they still provide plausible evidence that multiple micronutrients during pregnancy are more beneficial than iron–folic acid supplements for the mother and child. As such, these results are very encouraging and suggest that the program approaches tested in the Red River Delta should now be tested at a far larger scale. Multiple micronutrient supplements during pregnancy should be added to other interventions to provide a continuum of care from conception (or before) through 2 years of age. This continuum of care should include such interventions as periodic deworming and multiple micronutrient supplementation for mothers prior to pregnancy so that anemia is controlled before pregnancy, as well as the promotion of exclusive breastfeeding and adequate complementary feeding of their infants.

Conclusions

This nonblinded and nonrandomized trial of the effectiveness of a multiple micronutrient supplement during pregnancy as compared with the iron–folic acid supplement routinely provided in Vietnam resulted in an increase in birthweight and in height at 2 years of age in the districts provided with multiple micronutrients. There was no additional benefit in the district provided with gender training. Multiple micronutrient supplementation during pregnancy could be an important intervention to help reduce stunting rates in Vietnam.

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Multiple micronutrient supplementation during pregnancy in low-income countries: Review of methods and characteristics of studies included in the meta-analyses

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Abstract

This paper reports on the methods and characteristics of 12 studies from developing countries included in a meta-analysis of the impact of antenatal supplements of multiple micronutrients compared with iron–folic acid on micronutrient status, maternal nutritional status, birth outcomes, and neonatal survival.

Introduction

Poor nutrition during pregnancy has adverse consequences for the mother and child in both the short and the longer term. Ideally, women should enter pregnancy in a well-nourished state, but supplementation during pregnancy continues to be an important approach to addressing poor maternal nutrition. The World Health Organization (WHO) recommends universal distribution of iron–folic acid supplements to pregnant women in developing countries to prevent and treat iron-deficiency anemia. Many women suffer from multiple micronutrient deficiencies, not just iron deficiency [1]. In recognition of the potential importance to policy of widening the scope of current practice around supplementation, UNICEF, WHO, and the United Nations University (UNU) agreed on the formulation of a multiple micronutrient supplement for use in efficacy and effectiveness trials designed to assess the benefits and costs of replacing the iron–folic acid supplement [2]. The multiple micronutrient formulation is referred to as UNIMMAP (United Nations International Multiple Micronutrient Preparation); the composition of the supplement is given in **table 1**. A meeting was held at the Institute of Child Health in London in 2002 with most of the study investigators (those from the Burkina Faso study did not attend), where agreement was reached on a common study protocol among those using the UNIMMAP supplement [3]. A further progress review meeting was held in Bangkok in 2004 [4]. Where studies had already begun prior to the meeting, investigators agreed to try to standardize data collection to increase comparability of data outputs. There was an agreement to share data on completion.

In October 2005, a Systematic Review Team was commissioned by UNICEF/WHO/United Nations System Standing Committee on Nutrition (SCN) to undertake a review of published studies and the analysis of the studies where principal investigators had previously agreed to share their data. In addition to the investigators who participated in the Bangkok meeting, others also agreed to share their data.

An advisory board was established, including program managers and policy makers who had been associated with multiple micronutrient programs [1]. Terms of reference were agreed upon (available on request). After a preliminary analysis of the studies, a review meeting was held with the advisory board, the principal investigators, and the Systematic Review Team in Geneva in June 2006. The Systematic Review

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TABLE 1. Micronutrient composition of supplements used in the 12 trials

Micronutrient	UNIMMAP[a]	Mexico	Sarlahi, Nepal	Zimbabwe
Iron (mg)	30	62.4	60	0[b]
Zinc (mg)	15	12.9	30	15
Copper (mg)	2.0	—	2.0	1.2
Selenium (μg)	65	—	—	65
Magnesium (mg)	—	252	10	—
Iodine (μg)	150	—	—	—
Vitamin A (μg RE)	800	2,150 (IU)	1,000	3,000
β-Carotene (mg)	—	—	—	3.5
Vitamin B_1 (mg)	1.4	0.93	1.6	1.5
Vitamin B_2 (mg)	1.4	1.87	1.8	1.6
Folic acid (μg)	400	215	400	0
Niacin (mg)	18	15.5	20	17
Vitamin B_6 (mg)	1.9	1.94	2.2	2.2
Vitamin B_{12} (μg)	2.6	2.04	2.6	4.0
Vitamin C (mg)	70	66.5	100	80
Vitamin D (μg)	5	7.7	10	10
Vitamin E (mg)	10	5.7 (IU)	10	10
Vitamin K (μg)	—	—	65	—

RE, retinol equivalent; UNIMMAP, United Nations International Multiple Micronutrient Preparation

a. This formulation was used in all trials except those in Mexico; Sarlahi, Nepal; and Zimbabwe. In Guinea-Bissau, there was an additional group that received twice the amount of all nutrients except iron.

b. In Zimbabwe, iron–folic acid tablets were supplied separately as part of routine antenatal care and

Team presented summary reports of the published literature relating to the impact of multiple micronutrient supplementation during pregnancy on the mother's nutritional status, birth outcomes, and subsequent infant mortality. As a result of that meeting, participant principal investigators agreed to provide further information about their study designs so that as far as possible comparable information on each study population and background circumstances could be presented in the final report. Proposals for further analyses were made at this meeting, the results of which have been incorporated in the other papers presented in this supplement.

Methods

Studies included

The analyses reported in other papers in this issue are based on data from 12 studies. Nine of these (conducted in Bangladesh; Burkina Faso; China; Guinea-Bissau; Lombok, Indonesia; Indramayu, Indonesia; Janakpur, Nepal; Niger; and Pakistan) [5–13] used UNIMMAP (see **table 1**), and the other three (conducted in Mexico [14]; Sarlahi, Nepal [15]; and Zimbabwe [16]) used other multiple micronutrient supplements. The composition of the supplements used in these trials is summarized in **table 1**. All studies were randomized, controlled trials, with either individual or cluster randomization; some were factorial in design, where women were also randomized to additional interventions (behavior change, food, or treatments).

In most studies, the comparison (control) supplement was composed of 60 mg of iron and 400 μg of folic acid (iron–folic acid). The iron content of the UNIMMAP supplement was 30 mg. Women were given supplements either daily, weekly, fortnightly, or monthly, with compliance checked in a variety of ways. In Zimbabwe, women allocated to the control group were not given supplements but were encouraged to obtain standard antenatal care, which included iron–folic acid supplements.

Several studies had additional groups or different amounts of iron. In Bangladesh, there were two control supplements, one containing 60 mg of iron plus folic acid and the other 30 mg of iron pus folic acid. In the study in Sarlahi, Nepal, all women received vitamin A; the control group received only vitamin A while the other groups also received folic acid, folic acid plus iron, folic acid plus iron plus zinc, or a multiple micronutrient supplement. In the present analyses, we have compared the group receiving vitamin A, folic acid, and iron with the group receiving multiple micronutrients. In China, a third comparison group, which was not included in the meta-analyses, received folic acid only. In Lombok, Indonesia, the control supplement contained 30 mg of iron. In Guinea-Bissau, there were two intervention supplements: UNIMMAP and a supplement containing double the amount of the

UNIMMAP nutrients, except for iron, which remained at 30 mg. Only the single-supplement group was used in these analyses.

Some studies used a factorial design to assess the impact of other simultaneous interventions (details are described further in **table 3**). For the purposes of the analyses reported here, we have assumed that there was no interaction between these other interventions and the effect of supplementation, since all interventions were randomized. In Burkina Faso [9], there may have been an interaction between supplementation and antimalarial prophylaxis.

Meta-analysis

For each study, the raw data were reviewed and any queries were referred back to the principal investigators for clarification. Women who were known to be HIV-infected or who had multiple pregnancies were excluded from the analysis. In Burkina Faso and Mexico, some mothers (49 and 62 women, respectively) had more than one pregnancy during the study, and we included only the first birth in the analyses. For the mortality analyses, we also excluded women with fetal loss before 28 weeks and those for whom the outcome of the pregnancy was unknown. The analyses of birth outcomes were restricted to babies who were born alive after at least 28 weeks of gestation, who were measured within 72 hours after delivery, and whose gestational age at delivery was recorded as at least 28 weeks (196 days) and less than 45 weeks (315 days).

Results

Table 2 summarizes the characteristics of the trials for each study center. The number of mothers included ranged from 717 in Zimbabwe to 30,994 in Lombok, Indonesia. Data from a total of just over 52,000 women were collected and analyzed. In the birth outcome analyses, the numbers included in several trials were considerably smaller than the numbers in the total sample (and as tabulated in **Table 2**); for example, birth outcomes were analyzed for 13,270 of 30,994 women in Lombok, Indonesia, and 901 of 1,711 women in Pakistan. In some studies, it was difficult to perform measurements of birthweight within 3 days after delivery.

Ten trials enrolled participants in the first trimester, and two enrolled them in both the second and the third trimesters. In Burkina Faso, 35% of women were recruited in the first trimester. Eight studies did not exclude women on the basis of gestational age at enrollment; four studies (China, Niger, Mexico, and Janakpur, Nepal) excluded women on the basis of gestational age. Women were excluded if gestational age at enrollment was greater than 28 weeks in China, 12 weeks in Niger, 13 weeks in Mexico, and 20 weeks in Janakpur, Nepal.

The average maternal age was similar across studies (range of means, 21.5 to 26.0 years). Parity differed considerably between studies; in China 62% of women were having their first child, as compared with 19% in Niger. The reported levels of maternal education also varied widely among studies. In some studies (Sarlahi, Nepal; Pakistan; Burkina Faso; and Niger) approximately 80% to 90% of women had received no formal education, whereas in China this proportion was much lower. The two studies from Nepal differed in the proportion of women with no education (45% in Janakpur and 81% in Sarlahi).

Maternal height and body mass index (BMI) varied considerably. Mean height ranged from 148.7 cm in Mexico to 162.2 cm in Burkina Faso, and mean BMI ranged from 19.3 kg/m^2 in Sarlahi, Nepal, to 25.0 kg/m^2 in Zimbabwe.

Six studies (the two studies in Indonesia and those in China; Sarlahi, Nepal; Pakistan; and Niger) were cluster randomized, whereas the other six were individually randomized trials. In Lombok, Indonesia, the unit of cluster randomization was the midwife; in all other cluster-randomized trials, the village was the unit of randomization. The design of the study was taken into account in the way studies were analyzed.

Table 3 provides a description of the communities in each trial, with whatever information was available about other interventions or concurrent treatment protocols that may have been in place. In addition to supplements, the participants in most studies received some other form of intervention, allocated either in a factorial design or to the whole community. In Bangladesh, the supplement was given with a food supplement either early or late in pregnancy (as part of the Bangladesh Integrated Nutrition Programme [BINP]), and with or without metronidazole. In Indramayu, Indonesia, the women were given tablets on either a daily or a monthly basis to assess the impact on compliance. In Lombok, Indonesia, the whole community received a social marketing package, and each woman received a monthly visit from a community facilitator who provided health education. In Pakistan, women either received nutrition education or not, in addition to the supplement. In Sarlahi, Nepal, all women received antenatal care and nutrition advice at enrollment. In Janakpur, Nepal, anemic women and those described as night-blind received iron and vitamin A daily and were rechecked after 1 month. In Guinea-Bissau, severely anemic women were given additional iron, and all women received insecticide-impregnated bednets and weekly antimalarial prophylaxis. In Burkina Faso, in a factorial design, participants were also randomly assigned to receive either the malaria chemoprophylaxis recommended by health authorities (300 mg of chloroquine weekly) or intermittent preventive treatment (1,500 mg of sulfadoxine and 75 mg of pyrimethamine once in either the second or the third trimester).

TABLE 2. Summary data for the 12 trials

Location and reference Years of study No. of women randomized who had a known pregnancy outcome[a]	Micronutrient preparation Cluster or individual randomization	Control preparation	*No. of days from LMP to beginning of supplementation* Mean ± SD Range Missing observations	*Maternal age—yr* Mean ± SD Range Missing observations	*Maternal education—no. (%)* None Primary Secondary or higher Missing observations	*Parity—no. (%)* 0 1 or 2 > 2 Missing observations	*Maternal height—cm* Mean ± SD Range Missing observations	*Maternal BMI—kg/m²* Mean ± SD Range Missing observations	No. included in birth outcome analyses[b]	No. included in mortality analyses[c]
Asia										
Bangladesh [10] 2001–2004 2,412	UNIMMAP Individual	Iron 30 mg Folic acid 400 µg	102 ± 13 36–233 318	25.8 ± 5.9 14.0–50.0 2	740 (31) 529 (22) 1,133 (47) 10	813 (34) 1,168 (48) 431 (18) 0	149.8 ± 5.5 105.5–169.2 1	20.2 ± 2.7 13.9–35.4 7	1,818	2,412
China [5] 2002–2006 3,779	UNIMMAP Cluster	Iron 60 mg Folic acid 400 µg	96 ± 39 28–263 0	25.3 ± 4.4 12.9–41.3 12	215 (6) 1,025 (27) 2,526 (67) 13 (< 1)	2,345 (62) 1,421 (38) 13 (<1) 0	158.8 ± 5.2 130.0–178.0 36	20.9 ± 2.2 15.3–40.4 107	2,782	3,037
Indonesia (Indramayu) [6] 2001–2003 1,685	UNIMMAP Cluster	Iron 60 mg Folic acid 400 µg	101 ± 12 53–145 2	26.0 ± 6.3 13.0–45.0 0	161 (10) 1,143 (68) 381 (23) 0	692 (41) 769 (46) 224 (13) 0	151.3 ± 5.1 135.0–174.8 22	22.3 ± 3.7 13.9–41.4 24	1,435	1,598
Indonesia (Lombok) [8] 2001–2004 30,994	UNIMMAP Cluster	Iron 30 mg Folic acid 400 µg	146 ± 65 16–288 52	25.6 ± 6.1 14.0–50.0 1,455	3,710 (12) 15,274 (49) 11,032 (36) 978 (3)	11,797 (38) 12,946 (42) 5,436 (18) 815 (3)	149.9 ± 4.9 130.1–169.9 4,517	22.3 ± 2.9 13.5–41.2 8,007	13,270	28,643
Nepal (Sarlahi) [15] 1998–2001 1,699	Not UNIMMAP, iron 60 mg Cluster	Iron 60 mg Folic acid 400 µg Vitamin A 1,000 µg	80 ± 37 14–280 6	23.1 ± 5.6 12.0–42.0 6	1,375 (81) 135 (18) 178 (11) 11 (1)	442 (26) 665 (39) 583 (34) 9 (1)	150.1 ± 5.4 128.1–169.8 74	19.3 ± 2.0 14.3–26.7 75	1,287	1,699
Nepal (Janakpur) [11] 2002–2004 1,200	UNIMMAP Individual	Iron 60 mg Folic acid 400 µg	112 ± 17 84–177 0	21.5 ± 3.5 15.0–38.0 0	544 (45) 123 (10) 533 (44) 0	572 (48) 520 (43) 108 (9) 0	150.8 ± 5.4 126.8–168.9 3	19.8 ± 2.3 14.0–35.7 3	996	1,139

Pakistan [7] 2002–2004 2,699	UNIMMAP Cluster	Iron 60 mg Folic acid 400 μg	100 ± 27 44–188 338	25.7 ± 5.7 14.0–45.0 0	2,141 (79) 327 (12) 231 (9) 0	560 (21) 853 (32) 1,286 (48) 0	153.1 ± 6.0 108.0–182.0 56	21.4 ± 4.1 10.7–54.9 107	901	1,711
Africa										
Burkina Faso [9] 2003–2006 1,296	UNIMMAP Individual	Iron 60 mg Folic acid 400 μg	125 ± 53 0–263 13	24.4 ± 6 14–48 15	1,044 (81) 120 (9) 63 (5) 69 (5)	274 (21) 450 (35) 565 (44) 7 (1)	162.2 ± 5.9 143.4–184.0 16	20.9 ± 2.1 14.7–32.1 17	987	1,211
Guinea-Bissau [12] 2001–2002 1,424	UNIMMAP Individual	Iron 60 mg Folic acid 400 μg	158 ± 51 25–297 40	24.1 ± 5.6 13.0–48.0 3	317 (22) 622 (44) 71 (5) 414 (29)	334 (23) 391 (27) 289 (20) 410 (29)	160.4 ± 5.9 146.0–179.0 12	23.3 ± 3.4 14.8–41.8 220	600	1,091
Niger [13] 2003–2005 3,658	UNIMMAP Cluster	Iron 60 mg Folic acid 400 μg	72 ± 17 7–133 0	24.9 ± 6.1 13.0–45.0 0	3,294 (90) 317 (9) 33 (1) 14 (< 1)	723 (20)[d] 602 (16) 2302 (64) 31 (1)	158.0 ± 6.0 139.0–194.8 0	20.4 ± 2.3 11.8–33.8 0	2,321	2,896
Zimbabwe [16] 1996–1997 717	Not UNIMMAP, no iron or folic acid Individual	Usual care	205 ± 22 155–247 1	23.8 ± 5.3 14.4–43 0	Not recorded[e]	329 (46) 279 (39) 86 (12) 23 (3)	161.5 ± 5.7 143.0–179.4 7	25.0 ± 3.4 17.7–46.2 12	696	715
Central and South America										
Mexico [14] 1997–2000 811	Not UNIMMAP Individual	Iron 60 mg No folic acid	69 ± 20 32–141 4	22.9 ± 5.3 10.0–42.0 4	37 (5) 362 (45) 339 (42) 73 (9)	299 (37)[f] 500 (62) 12 (< 1)	148.6 ± 4.9 130.2–162.6 3	24.1 ± 4.1 15.8–46.4 4	583	611

BMI, body mass index; LMP, last menstrual period; UNIMMAP, United Nations International Multiple Micronutrient Preparation

a. Women who were known to be HIV-infected or to have multiple pregnancies were excluded. Only the first pregnancy for each woman was included.

b. Additional exclusions were fetal loss before 28 weeks, stillbirths, infants with gestational age at delivery < 189 or > 314 days, and infants measured > 72 hours after birth.

c. Additional exclusions were fetal loss and unknown live or stillborn status

d. In Niger, parity was classified as 0, 1, or higher than 1.

e. There were no data on maternal education in Zimbabwe.

f. In Mexico, parity was classified as 0 or 1 or more.

TABLE 3. Details of study populations

Study	Study details	Other interventions, treatments, and exclusions
	Asia	
Bangladesh [10]	Conducted in Matlab, a poor rural subdistrict in the east central plain of Bangladesh. Women were recruited as part of the routine Demographic Health Surveillance. Compliance: each woman received a month's supply of multiple micronutrients at her monthly antenatal checkup.	Women were allocated to either early or late (usual) food supplementation. Food packets containing roasted rice powder (80 g), roasted lentil powder (40 g), molasses (20 g), and soy oil (12 mL) provided 600 kcal (2,512 kJ) of energy. Supplementation was provided with or without metronidazole to prevent bacterial vaginosis.
China [5]	Two poor rural counties (with urban and rural communities) in Shaanxi Province of northwest China. 561 villages were cluster randomized. Compliance: at enrollment, each woman received 15 capsules and was instructed to take 1 capsule daily. The village doctor visited every 2 weeks to provide more supplements and record the number of remaining capsules.	Women were excluded if they were at 28 weeks or more of gestation at enrollment, were taking other supplements, or were seriously ill.
Indonesia (Indramayu) [6]	Two rural subdistricts covering 26 villages in Indramayu, West Java. Cluster randomized by 160 blocks within villages. Compliance: monthly pill count.	Groups were assigned to either daily ("efficacy") or monthly ("effectiveness") allocation of tablets.
Indonesia (Lombok) [8]	All villages outside the capital city on the island of Lombok. Randomization based on 262 midwives serving the population. Compliance: women replenished their capsules each month from midwives who logged date and previous consumption by inspecting blister strips. Community facilitator also inspected blister strips during home visits.	Attended deliveries were supported by trained staff. Social marketing was provided to the whole community; women were visited monthly by community facilitators, who provided health education and promoted prenatal care and skilled care at delivery.
Nepal (Sarlahi) [15]	Southeastern plains District of Sarlahi. Study area was 30 village development communities divided into 426 small units. Evidence of vitamin A, iron, and zinc deficiency in pregnant women. Compliance: sector workers delivered supplements twice weekly to women in their homes.	All women received counseling on antenatal care and nutrition at enrollment. They were encouraged to take iron supplements. Deworming (albendazole) medicine was offered in 2nd and 3rd trimesters. Women received tetanus toxoid vaccination twice during pregnancy, a safe birthing kit, and a flannel blanket for the newborn.
Nepal (Janakpur) [11]	All women attending an antenatal clinic at Janakpur zonal hospital. Women were eligible if gestation ≤ 20 weeks; singleton pregnancy; no notable fetal abnormality; no existing maternal illness severe enough to compromise pregnancy outcome; and participant lived in Dhanusha or adjoining Mahottari, accessible for home visits. Compliance: contact visit every 2 weeks; compliance checked by a combination of monthly clinic visits and monthly home visits.	In the event of significant illness, the participant was seen by a consultant obstetrician or doctor. If a participant's enrollment hemoglobin concentration was less than 70 g/L, she was given an extra 60 mg of iron daily and anthelminthic treatment, and her hemoglobin was rechecked after 1 month; if a participant described night-blindness at any time, she was given 2,000 µg of vitamin A daily and referred for medical follow-up.

continued

TABLE 3. Details of study populations *(continued)*

Study	Study details	Other interventions, treatments, and exclusions
Pakistan [7]	Urban population in Karachi and villages of Kot Diji District (rural Sindh). Allocated urban and rural areas to 28 discrete clusters (16 rural, 12 urban) based on household characteristics, socioeconomic criteria, and geographic location. Each cluster was allocated a community health worker who covered about 600–700 households and 3,500–4,000 women. Compliance: community health workers provided 2-week supply of supplements (multiple micronutrients or iron–folic acid) and did a tablet count and stock replenishment at every 2-week visit.	Community outreach: in one group, the supplements were provided along with basic nutrition and antenatal care messages (focusing on the importance of maternal nutrition, antenatal care, and micronutrient supplements to avert maternal anemia) through home visits. In the other, the home visits were complemented with additional quarterly community-based group sessions held in the houses of community participants who volunteered.
	Africa	
Burkina Faso [9]	Houndé health district (southwest of Burkina Faso) in area covered by 2 health centers. Only exclusion criterion was plan to leave area in next 2 years. Compliance: tablet intake was directly observed at daily home visits. Tablets were given in advance only for short scheduled absences. Home visitors updated reporting sheets daily, recording tablet intake, morbidity, and pregnancy complications.	Participants were also randomly assigned to receive either the malaria chemoprophylaxis recommended by health authorities (300 mg of chloroquine weekly) or intermittent preventive treatment (1,500 mg of sulfadoxine and 75 mg of pyrimethamine once in the 2nd and 3rd trimesters). In case of maternal illness, appropriate treatments were provided according to national guidelines. Severely anemic women (hemoglobin < 70 g/L, without dyspnea) received ferrous sulfate (200 mg) plus folic acid (0.25 mg) twice daily for 3 months, whatever their allocation group. All participants also received 400 mg of albendazole in the 2nd and 3rd trimesters. If malaria occurred in spite of chemoprophylaxis, quinine (300 mg, 3 times a day) was given for 5 days. Vitamin A (200,000 IU) was given to all women after delivery, in conformity with the national recommendations.
Guinea-Bissau [12]	Semiurban area of Bissau: women were identified through monthly pregnancy surveillance in the Bandim Health Project and recruited until late pregnancy. Compliance: women were given containers with 25 tablets; tablets were counted every 2 weeks and replenished during home visits.	Women with severe anemia (hemoglobin < 70 g/L) were given an additional 60 mg of iron daily. All women received insecticide-impregnated bednets at inclusion and were provided weekly antimalarial prophylaxis with chloroquine phosphate throughout pregnancy. Those with > 10 parasites per 200 leukocytes at inclusion were offered chloroquine treatment.
Niger [13]	Rural Niger in the north of the administrative region of Maradi. 78 villages within the coverage of the 17 health centers of Mayahi District were included. All of the villages — not individuals — were randomly assigned to the control or intervention group. Women were eligible to participate if they lived in a selected village and had amenorrhea for < 12 weeks. Compliance: 35 tablets were given monthly; compliance was measured by pill count. At each subsequent visit, the remaining pills were counted and the number of missing tablets was replenished for next month and recorded.	Women with night-blindness and/or clinical signs of severe anemia received appropriate medical treatment and were excluded from the study. Behavior change communication activities were conducted to increase awareness and encourage participation in the study and adoption of better lifestyles, including feeding practices and rest during pregnancy. Women received a free package of reproductive health services, including malaria chemoprophylaxis and appropriate case management.

continued

TABLE 3. Details of study populations *(continued)*

Study	Study details	Other interventions, treatments, and exclusions
Zimbabwe [16]	Mbare residential area of Harare. Women were at weeks 22 to 36 of gestation at enrollment. Allocation to daily multiple micronutrient supplement or placebo based on simple, blocked randomization. All women received iron–folic acid as part of routine care (not measured). The present analysis included only HIV-negative women. Compliance: after baseline examination, each participant was given a container and instructed to take 1 tablet with a meal every morning until delivery. For women delivering an infant at the Edith Oppermann Maternity Hopsital (EOMH), the remaining tablets were counted and the number taken was used as a measure of compliance.	
Central and South America		
Mexico [14]	Near the city of Cuernavaca in Morelos. All new pregnancies were identified by a routine home-based surveillance system in which fieldworkers visited women of reproductive age every 5 weeks. Women who agreed to participate were then randomly allocated to either the multiple micronutrient or the iron-only group. Exclusion criteria: > 13 weeks of pregnancy at recruitment, use of micronutrient supplements, refusal to participate. Compliance: the first supplement was consumed at the study headquarters, after which trained workers visited the women's homes 6 days per week until delivery to administer supplements and record their consumption.	

Compliance was measured in different ways. In Sarlahi, Nepal, women were contacted twice weekly by a sector distributor to monitor intake; in Janakpur, Nepal, and in Guinea-Bissau, the number of pills consumed was counted at each fortnightly visit; in Zimbabwe, there was a simple pill count after delivery. In Burkina Faso, tablet intake was directly observed in daily home visits. The average number of supplements reported as consumed was 165 in China; 164 in Mexico; 157 in Janakpur, Nepal; 152 in Sarlahi, Nepal; 124 in Lombok, Indonesia; 107 in Indramayu, Indonesia; 114 in Burkina Faso; 81 in Guinea-Bissau; and 62 in Zimbabwe.

Discussion

More than 52,000 women from 12 studies have been included in the meta-analyses; one study (Lombok, Indonesia) contributed over half of all the data, and two studies each contributed fewer than a thousand women. This variation in sample size needs to be considered when reviewing the findings from the meta-analysis.

The studies included in the meta-analyses were primarily from Asia and Africa, with only one from Latin America. The average birthweights differed by more than 500 g between the studies in Bangladesh and China and by about 150 g between the two studies in Nepal [17]. The average birthweights in the four African studies ranged from 2,900 to 3,050 g. There were large differences among studies in baseline nutritional status, with women in Bangladesh, Indonesia, Mexico, Nepal, and Pakistan being nearly 10 cm shorter than women in Africa and China. The mean BMI was highest in Guinea-Bissau, Mexico, and Zimbabwe and lowest in Nepal. There were also large differences in parity and levels of education among the women from different study centers. All these factors suggest differences in the living and public health circumstances of the women that may alter the impact of the supplementation on birth outcomes and mortality.

It is also possible that both supplements improved outcome measures compared with the general populations from which the women were recruited. Most studies compared a multiple micronutrient supplement containing iron with an iron–folic acid supplement containing twice as much iron. One comparison group (Sarlahi, Nepal) received vitamin A as well as iron–folic acid. In the studies in Lombok, Indonesia, and in Bangladesh, the control group received 30 mg of iron, as compared with 60 mg in other studies.

The gestational age at which supplementation started, and thus the total exposure to supplementation, varied considerably across studies. Compliance was measured with different levels of accuracy. Further, the fact that four studies excluded women recruited after certain gestational dates and eight studies did not adds to the potential variation in study findings. There is a potential for interaction between the gestational age at which supplements commenced and the nutritional status of the mother at conception on the impact the supplementation had on outcomes. Studies were not a priori designed to assess this interaction, and although these factors have been included in analyses in subsequent papers, there is a strong possibility that these interactions have not been correctly disentangled.

Taken together, the differences in the wider environments in which women lived in each country, in baseline nutritional status, and in compliance (time of introduction and amount of supplement consumed) could all influence the way the supplements affected outcomes. This needs to be considered when interpreting the findings of the meta-analyses.

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Impact of multiple micronutrient versus iron–folic acid supplements on maternal anemia and micronutrient status in pregnancy

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Abstract

Background. *Multiple micronutrient supplements could increase hemoglobin and improve micronutrient status of pregnant women more than iron supplements alone or iron with folic acid .*

Objective. *To compare the effects of multiple micronutrients with those of iron supplements alone or iron with folic acid, on hemoglobin and micronutrient status of pregnant women.*

Methods. *Studies were identified in which pregnant women were randomized to treatment with multiple micronutrients, or with iron with or without folic acid. A pooled analysis was conducted to compare the effects of these supplements on maternal hemoglobin, anemia, and micronutrient status. Effect size was calculated for individual and combined studies, based on mean change from baseline to final measure in the group receiving iron, with or without folic acid, minus the mean change in the group, divided by the pooled standard deviation of the two groups. The effect on the relative risk of anemia or iron deficiency was calculated as the probability of anemia or iron deficiency in the group receiving multiple micronutrients divided by the probability in the group receiving iron, with or without folic acid.*

Results. *Multiple micronutrient supplements had the same impact on hemoglobin and iron status indicators as iron with or without folic acid. There was no overall effect on serum retinol or zinc. In the only study in which status of other micronutrients was analyzed, a high prevalence of multiple deficiencies persisted in the group receiving multiple micronutrients provided with daily recommended intakes of each nutrient.*

Conclusions. *Multiple micronutrient supplements increased hemoglobin synthesis to the same extent as supplementation with iron with or without folic acid, although often they contained lower amounts of iron. The amount of supplemental iron and other nutrients that can enable pregnant women with micronutrient deficiencies to achieve adequate status remains to be determined.*

Key words: Folic acid, iron, multiple micronutrients, pregnancy, supplements

Introduction

Maternal consumption of multiple micronutrient supplements during pregnancy should improve indicators of maternal micronutrient status more than the iron supplements, with or without folic acid, more commonly provided, but there has been no previous review of the extent to which supplements providing close to the daily recommended intake of multiple micronutrients affect nutritional status indicators. Multiple micronutrient supplements should help to reduce anemia, because other nutrients that are often lacking in the diets of pregnant women in poor populations, including vitamin A, riboflavin, and vitamins B_6 and B_{12}, are also needed for hemoglobin synthesis. Improving maternal status of other micronutrients could also benefit pregnancy outcome, infant micronutrient stores

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at birth, and breast milk content of the nutrients [1].

The purpose of the present analysis is to determine whether multiple micronutrient supplements have greater effects on anemia and micronutrient status during pregnancy than do supplements of iron, with or without folic acid.

Methods

Data on micronutrient status were obtained, when available, from the United Nations International Multiple Micronutrient Preparation (UNIMMAP) supplementation studies. However, this article differs from the other meta-analyses reported in this Supplement because of the inclusion of several studies that specifically examined micronutrient outcomes; few of the UNIMMAP studies had much data on micronutrient status. The sources of available data on hemoglobin and indicators of iron and vitamin A status and micronutrient contents of the supplements are shown in **table 1** [2–16]. In most of the studies, the multiple micronutrient supplement contained at least 11 or 12 micronutrients, although in some only 1 or 2 micronutrients were added to the iron and folic acid. In 5 (UNIMMAP studies) of the 13 studies analyzed here, there was twice as much iron (60 mg) in the supplement containing iron, with or without folic acid, as in the multiple micronutrient supplement (30 mg). Because a relatively small amount of data was available on other nutritional status indicators, the sources of this information are referred to in the relevant sections of the text.

Effect sizes were calculated as the mean of the control group (i.e., supplemented with iron, with or without folic acid) minus the mean of the group receiving multiple micronutrients divided by the pooled standard deviation of the two groups. When available, the effect size was based on the changes from baseline to final measurement and the standard deviations of the changes. When this information was unavailable, the effect size was calculated from the mean and standard deviation of the final value. Confidence intervals were calculated for each effect size; intervals that do not include 1.0 are statistically significant. An effect size of 0.2 was considered small, 0.5 moderate, and 0.7 large.

For anemia and iron-deficiency anemia, the effect of multiple micronutrients compared with that of iron, with or without folic acid, on the relative risk of these conditions was calculated as the probability of anemia or iron deficiency in the group receiving multiple micronutrients divided by the probability of anemia or iron deficiency in the group receiving iron, with or without folic acid.

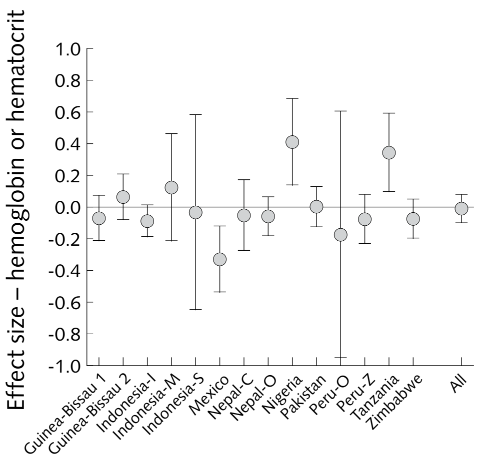

FIG. 1. Effect sizes for hemoglobin or hematocrit in the groups receiving multiple micronutrients vs. the groups receiving iron, with or without folic acid. Guinea-Bissau = ref. 2, 1 = 1 RDA, 2 = 2 RDA; Indonesia I = ref. 3, M = ref. 4, S = ref. 5; Nepal C = ref. 7 and Nepal O = ref. 8; Peru O = ref. 11 and Peru Z = ref. 12.

Results

Anemia and iron status

All studies, including all the UNIMMAP trials, had data on hemoglobin, except for one that recorded hematocrit [9]. Among the individual trials, the only statistically significant effect sizes were found in Mexico (a negative effect, with a smaller change in hemoglobin during pregnancy in the group receiving multiple micronutrients than in the iron group) and in Nigeria and Tanzania (positive effects) (**fig. 1**). Overall, as indicated on the right of **figure 1**, multiple micronutrients did not increase hemoglobin more than iron, with or without folic acid, alone. The same was true of iron status, with the multiple micronutrients

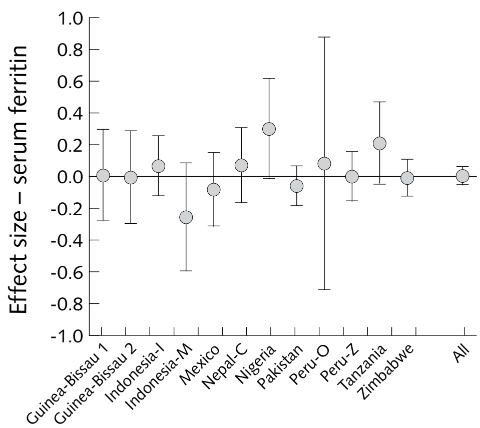

FIG. 2. Effect sizes for serum ferritin in the groups receiving multiple micronutrients vs. the groups receiving iron, with or without folic acid

TABLE 1. Sources of data on indicators of iron and vitamin A status

Study	Control	Multiple micronutrients	Indicators measured					
			Hemoglobin	Ferritin	Anemia	Iron-deficiency anemia	Serum transferrin receptor	Retinol
Guinea-Bissau [2]	Iron 60 mg Folic acid 400 μg	Iron 30 mg 14 micronutrients UNIMMAP[a]	√	√				√
Guinea-Bissau [2]	Iron 60 mg Folic acid 400 μg	Iron 30 mg 2 RDA of 14 micronutrients UNIMMAP						
Indonesia [3]	Iron 60 mg Folic acid 400 μg	Iron 30 mg 14 micronutrients UNIMMAP	√					
Indonesia [4]	Iron 120 mg weekly	Iron 120 mg weekly Folic acid Vitamin A	√	√	√			√
Indonesia [5]	Iron 50 mg Folic acid 250 μg	Iron 50 mg Vitamin A Vitamin B_2 Folic acid All anemic	√					
Mexico [6]	Iron 60 mg	Iron 62 mg 12 micronutrients	√	√	√	√	√	
Nepal [7]	Iron 60 mg Folic acid 400 μg	Iron 60 mg 14 micronutrients	√	√	√	√	√	√
Nepal [8]	Iron 60 mg Folic acid 400 μg	Iron 30 mg UNIMMAP	√		√			√
Nigeria [9]	Iron 50 mg Folic acid 5,000 μg	Iron 50 mg 5 micronutrients	√[b]	√				
Pakistan [10]	Iron 60 mg Folic acid 400 μg	Iron 30 mg UNIMMAP	√	√				
Peru [11, 12, 13]	Iron 60 mg	Iron 60 mg Folic acid Zinc	√	√			√	
Tanzania [14]	Iron 60 mg through health center Placebo	Iron 10 mg 10 micronutrients Iron 60 mg through health center	√	√	√	√		√
Indonesia [15]	Iron 30 mg	Iron 30 mg Folic acid β-carotene Zinc	√	√				√
Zimbabwe [16]	Iron Folic acid through health system	13 micronutrients Iron Folic acid through health system	√	√				√

a. The United Nations International Multiple Micronutrient Preparation (UNIMMAP) supplement contains 30 mg of iron, 15 mg of zinc, 2 mg of copper, 65 μg of selenium, 150 μg of iodine, 800 μg RE of vitamin A, 1.4 mg of vitamin B1, 1.4 mg of vitamin B_2, 400 μg of folic acid, 18 mg of niacin, 1.9 mg of vitamin B_6, 2.6 μg of vitamin B_{12}, 70 mg of vitamin C, 200 IU of vitamin D, and 10 mg of vitamin E.
b. Measured by hematocrit.

failing to increase serum ferritin more than iron, with or without folic acid, in any study or overall (**fig. 2**). Transferrin receptors were measured in only three locations. In Nepal [7], there was no significant difference in the change in concentration between the group that received iron plus folic acid plus vitamin A and the group that received multiple micronutrients, but both groups had lower concentrations (better iron status) at the end of the study than groups that received folic acid plus vitamin A alone, with no iron. Similarly, the change in transferrin receptor concentrations was the same in pregnant women given iron, with or without folic acid, plus vitamin A as in those given iron, with or without folic acid, alone [4]. In Peruvian pregnant women, the final mean serum transferrin receptor concentrations did not differ between a group receiving iron, with or without folic acid, and a group receiving iron, with or without folic acid, plus zinc, and both of these groups had significantly lower final concentrations than a control group that did not receive iron [11].

The relative risk of anemia could be compared in four studies [4, 7, 8, 13] and was not different in the group receiving multiple micronutrients or overall, from that in the groups receiving iron, with or without folic acid. The risk of iron-deficiency anemia could be compared only in Mexico [6], Nepal [7], and Tanzania [13]. In none of these trials was the risk different by supplement group.

Information is almost completely lacking on the effect of maternal multiple micronutrient supplementation in pregnancy on infant hemoglobin or iron status. In the only three studies that measured hemoglobin, hematocrit, or serum ferritin in cord blood, there was no difference between the multiple micronutrient and the iron–folic acid groups [9, 11, 12].

Vitamin A and other micronutrients

Of the eight trials that had data on serum retinol concentrations, one found a significant positive effect of the multiple micronutrient supplement [3] and one a significant negative effect [4], but there was no effect overall for the trials combined (**fig. 3**). There was significant heterogeneity of the serum retinol response to multiple micronutrients among the trials, perhaps not surprisingly, since the dose varied across studies.

Changes in serum zinc were measured in only three studies. Adding zinc to iron supplements, with or without folic acid, increased maternal serum zinc concentrations in Peru [13], although the same group observed that women supplemented with iron plus folic acid, or iron plus folic acid plus zinc, had lower serum zinc concentrations than a group that had no prenatal supplements [11]. The two other studies found no difference in serum zinc concentrations of pregnant women when zinc was provided compared with iron alone, with or without folic acid [4, 16].

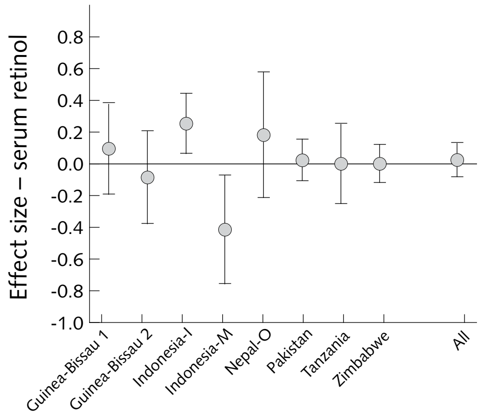

FIG. 3. Effect sizes for serum retinol in the groups receiving multiple micronutrients vs. the groups receiving iron, with or without folic acid

The most thorough examination of maternal micronutrient status was conducted in one study in Nepal [17]. The supplements (400 μg of folic acid; 400 μg of folic acid plus 60 mg of iron; 400 μg of folic acid plus 60 mg of iron plus 30 mg of zinc; or multiple micronutrients containing the same amounts of folic acid, iron, and zinc plus 11 other micronutrients) were provided prior to conception, and final measures of maternal status were obtained at 32.6 weeks of pregnancy. Serum folate was significantly increased in all of the groups receiving supplements in comparison with the control group receiving vitamin A alone. However, only the multiple micronutrient supplement increased serum vitamin B_{12}, riboflavin, vitamin B_6, 25-hydroxyvitamin D, and zinc compared with the values in the control group. In spite of these overall significant improvements in micronutrient status, a high proportion of the women were still deficient in all nutrients (except vitamin A) in the third trimester, especially vitamin B_{12} (65% of women), vitamin B_6 (66%), riboflavin (37%), and zinc (87%). This raises the question of whether the micronutrient content of the supplements, which contained approximately the recommended daily intake of each nutrient and were taken daily from early pregnancy, was high enough. Subclinical infections may also have affected the micronutrient status markers [17, 18].

Discussion

Comparisons among the studies reviewed in this analysis should be made with caution, because of differences in the composition of micronutrient supplements, the frequency and duration of supplementation, and initial rates of anemia and iron deficiency. However, some general conclusions can be drawn. Most of the studies limited their assessment of nutritional status to measures of hemoglobin and iron status. Overall, the multiple micronutrients produced the same effect as iron, with or without folic acid, on hemoglobin concentrations, anemia, and iron status, although many of the multiple micronutrient supplements contained lower amounts of iron. When maternal iron supplementation is started relatively early in pregnancy (i.e., during the second trimester at the latest), it is unlikely that 60 mg of iron will be more effective for improving hemoglobin or iron status than 30 mg [19, 20]. The analysis also indicates that adding the other micronutrients did not impair the efficacy of the iron supplements.

The amount of vitamin A contained in the supplements did not increase serum retinol concentrations. This was perhaps because of insufficient fat in the diet to enable absorption, inadequate amounts of vitamin A in the supplement, or poor sensitivity of serum retinol as the indicator.

Only one study, conducted in rural Nepal, measured more than a few nutritional status indicators [17]. This study revealed that a high prevalence of multiple micronutrient deficiencies persisted in late pregnancy, even though the multiple micronutrient supplement was provided throughout gestation. Although rural Nepal may have a greater micronutrient deficiency problem than many developing countries, these results do illustrate the need to include other micronutrients in supplements for such populations, and raise the possibility that the doses used—typically around the recommended intake for pregnant women—were not sufficient to restore nutritional status to normal. In this regard, it is noteworthy that other studies have safely provided substantially higher quantities of some micronutrients in multiple micronutrient supplements for pregnant women [2, 18]. More work is needed to determine the dose of each specific micronutrient that is sufficient to improve, and ideally restore, maternal nutritional status during pregnancy, without producing any adverse effects. This has never been studied systematically but could be feasible to study in smaller groups of women than in the larger pregnancy outcome trials, if nutritional status is studied as the outcome of interest rather than measures such as birthweight. If possible, samples from the Guinea-Bissau trial [2] should be analyzed for indicators of multiple micronutrient status, as the multiple micronutrient supplement in that trial was given both at the recommended daily allowance level and at twice that dose (except for iron).

Conclusions

The effects of multiple micronutrients on maternal hemoglobin, hematocrit, and iron status did not differ from the effects of iron alone, with or without folic acid. There was no significant effect of the multiple micronutrients on serum retinol or zinc. The persistence of deficiency of many nutrients indicates that at present there is inadequate information from which to develop the most effective multiple micronutrient supplements for pregnant women consuming poor-quality diets, although it is unlikely that one formulation will be ideal for all. Attention to this question should take priority, as it is doubtful that providing iron and folic acid alone will be adequate to meet the needs of most of these women during pregnancy.

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Multiple micronutrient supplementation during pregnancy in low-income countries: A meta-analysis of effects on birth size and length of gestation

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Abstract

Background. *Multiple micronutrient deficiencies are common among women in low-income countries and may adversely affect pregnancy outcomes.*

Objective. *This meta-analysis reports the effects on newborn size and duration of gestation of multiple micronutrient supplementation mainly compared with iron plus folic acid during pregnancy in recent randomized, controlled trials.*

Methods. *Original data from 12 randomized, controlled trials in Bangladesh, Burkina Faso, China, Guinea-Bissau, Indonesia, Mexico, Nepal, Niger, Pakistan, and Zimbabwe, all providing approximately 1 recommended dietary allowance (RDA) of multiple micronutrients to presumed HIV-negative women, were included. Outcomes included birthweight, other birth measurements, gestation, and incidence of low birthweight (LBW) (< 2,500 g), small-for-gestational age birth (SGA, birthweight below the within-each-population 10th percentile), large-for-gestational age birth (LGA, birthweight above the within-each-population 90th percentile), and preterm delivery (< 37 weeks).*

Results. *Compared with control supplementation (mainly with iron–folic acid), multiple micronutrient supplementation was associated with an increase in mean birthweight (pooled estimate: +22.4 g [95% CI, 8.3 to 36.4 g]; p = .002), a reduction in the prevalence of LBW (pooled OR = 0.89 [95% CI, 0.81 to 0.97]; p = .01) and SGA birth (pooled OR = 0.90 [95% CI, 0.82 to 0.99]; p = .03), and an increase in the prevalence of LGA birth (pooled OR = 1.13 [95% CI, 1.00 to 1.28]; p = .04). In most studies, the effects on birthweight were greater in mothers with higher body mass index (BMI). In the pooled analysis, the positive effect of multiple micronutrients on birthweight increased by 7.6 g (95% CI, 1.9 to 13.3 g) per unit increase in maternal BMI (p for interaction = .009). The intervention effect relative to the control group was + 39.0 g (95% CI, +22.0 to +56.1 g) in mothers with BMI of 20 kg/m^2 or higher compared with –6.0 g (95% CI, –8.8 to +16.8 g) in mothers with BMI under 20 kg/m^2. There were no significant effects of multiple micronutrient supplementation on birth length or head circumference nor on the duration of gestation (pooled effect: +0.17 day [95% CI, –0.35 to +0.70 day]; p = .51) or the incidence of preterm birth (pooled OR = 1.00 [95% CI, 0.93 to 1.09]; p = .92).*

Conclusions. *Compared with iron–folic acid supplementation alone, maternal supplementation with multiple micronutrients during pregnancy in low-income countries resulted in a small increase in birthweight and a reduction in the prevalence of LBW of about 10%. The effect was greater among women with higher BMI.*

Key words: Birth outcomes, birthweight, iron–folic acid, maternal body mass index, meta-analysis, multiple micronutrients, pregnancy, preterm delivery

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Introduction

Low birthweight (LBW), resulting from restricted fetal growth, preterm birth, or both, is a persistent problem in disadvantaged populations of low-income countries and is associated with increased infant morbidity and mortality, childhood stunting and cognitive impairment, and an increased risk of adult chronic disease [1–4]. Short maternal height (resulting from undernutrition when the mother was herself a fetus and child) and low maternal body weight (resulting from undernutrition before and during pregnancy) are well-established causes of LBW [5, 6]. Randomized, controlled trials have shown that protein and energy supplementation during pregnancy has a positive effect on birthweight, assessed at 37.62 g (–0.21 to 75.45 g) in the latest meta-analysis [7]. The small size of this effect may be due to limiting micronutrient deficiencies.

Mothers in low-income countries frequently have inadequate micronutrient intakes [8]. Iron–folic acid supplements for pregnant women have been routinely recommended for use in most countries for several decades, but there is no consistent evidence of improvement in birthweight or other birth outcomes. Given the requirement for a whole range of micronutrients in metabolic pathways, repletion of only one or two micronutrients in a woman who has multiple deficiencies is likely to be ineffective. Since distribution systems are already in place to deliver iron–folic acid tablets to pregnant women, multiple micronutrient supplements may be a relatively cost-effective way of improving pregnancy outcomes in undernourished populations [8]. A Cochrane Collaboration systematic review of multiple micronutrient supplementation trials in pregnancy, published in 2006, concluded that compared with iron-folate supplementation, there were reductions in LBW and small-for-gestational age (SGA) births, but these were not statistically significant [9]. This paper is a review and meta-analysis of birth outcomes from 12 recently conducted randomized, controlled trials in 10 low-income countries in Asia (Bangladesh [10], China [11], Indonesia [12, 13], Nepal [14, 15], and Pakistan [16]), Africa (Burkina Faso [17], Guinea-Bissau [18], Niger [19], and Zimbabwe [20]), and Central and South America (Mexico [21]).

Methods

Details of the 12 randomized, controlled trials and the exact composition of the multiple micronutrients and control tablets used in each study are provided in the accompanying paper by Margetts et al. [22]. In brief, the investigators recruited mainly HIV-negative women, started supplementation in pregnancy rather than preconceptionally, and used a multiple micronutrient formulation that delivered approximately 1 RDA (recommended dietary allowance) daily. Nine studies used the United Nations International Multiple Micronutrient Preparation (UNIMMAP) of UNICEF/United Nations University/World Health Organization, while the studies in Mexico, Nepal (Sarlahi), and Zimbabwe used slightly different preparations. The UNIMMAP tablets contain 30 mg of iron, whereas the control tablets in most of the studies using the UNIMMAP supplement provided 60 mg of iron [22]. In trials with more than one control group, we compared outcomes in the group receiving multiple micronutrients with outcomes in the control group providing iron–folic acid in the doses closest to those in the multiple micronutrient supplement. Six trials were cluster randomized (China, Indonesia [Indramayu], Indonesia [Lombok], Nepal [Sarlahi], Pakistan, and Niger).

Outcomes included birthweight, other birth measurements (length, head circumference, and mid-upper-arm circumference, where available), duration of gestation, and incidence of LBW (< 2,500 g), small-for-gestational-age (SGA) birth (birthweight below the within-each-study-population 10th percentile for gestational age), large-for-gestational age (LGA) birth (birthweight above the within-each-study-population 90th percentile), and preterm delivery (gestation < 37 weeks). We used within-population definitions of SGA and LGA rather than using an external reference, because commonly used external references are derived from populations in high-income countries and would have produced very high rates of SGA and negligible rates of LGA; we were interested in the effect of the supplement on extremes of birthweight within each population.

Statistical methods

We initially excluded mothers who were known to be HIV positive, known to be carrying multiple pregnancies, or were assigned to intervention groups other than the selected control group or the group receiving multiple micronutrients. Only one pregnancy per woman (the earliest) was included. For the analyses reported in this paper on birth outcomes, the analysis was further restricted to live births occurring after at least 28 weeks of gestation, babies measured within 72 hours after delivery, and babies whose gestational age at delivery was recorded as at least 28 weeks (196 days) and less than 45 weeks (315 days). For the outcomes SGA, LGA, gestational age, and preterm delivery, the sample was further restricted to exclude babies with implausible combinations of birthweight and gestational age (see below). Random-effects meta-regression models were used, adjusted for cluster design where appropriate, to derive treatment effects in each trial, pooled values, and forest plots. Effect size estimates were also derived after adjustment for the infant's sex and maternal age, weight (at recruitment), parity, and education. Heterogeneity between studies was tested with the use of the *I*-square statistic with a significance level set at < .10. Interaction tests were used to explore differences in supplementation effects according to maternal age, parity, height, and BMI and the gestational age at which supplementation started. All were treated as continuous variables, except for parity, which was categorized in two ways, into two groups (nulliparous versus multiparous women) and into three groups (parity of 0, 1, or ≥ 2). Both linear and quadratic interactions were tested. Maternal BMI was measured at recruitment, which occurred at various gestational ages and was therefore adjusted to a gestational age of 105 days (15 weeks) using linear regression analysis, within each study.

Exclusion of implausible gestational age data

Gestational ages based on the date of the last menstrual period are often underestimated in population studies [23–27]. Many combinations of birthweight and gestational age were implausible in the data from the 12 trials (**fig. 1**), suggesting frequent underestimation of gestational age. This phenomenon was particularly marked in Pakistan and Niger, leading to an implausibly high incidence of preterm delivery (29% and 41%, respectively). To overcome this problem, a "generic" fetal growth curve was constructed using sex-specific 10th, 50th, and 90th percentile values for birthweight at gestational ages of 27 to 45 weeks from an external reference, based on more than 2 million births in the United States [28]. From this curve, mean (± SD) birthweight values at different gestational ages were derived. This curve was then applied to data from each of the 12 trials, scaled down according to the full-term birthweight (38 to 40 weeks) in each location. Mean (± SD) values for birthweight at all gestational ages were derived for each study. Babies whose birthweight was more than 3 SD above or below the gestation-specific mean were excluded from analyses of outcomes involving gestational age (SGA, LGA, gestational length, and preterm deliveries). Data excluded in this way are indicated by open circles in **figure 1**.

Results

The numbers of mothers included in the analysis of birth outcomes ranged from 583 in Mexico to 13,270 in Indonesia (Lombok). The mean birthweight (babies in both trial groups) ranged from 2,649 g in Bangladesh to 3,198 g in China, and mean gestation ranged from 263 days (37.6 weeks) in Niger to 279 days (39.9 weeks) in China. Additional details on maternal anthropometry and other characteristics are given in **table 2** of the paper by Margetts et al. in this issue [22].

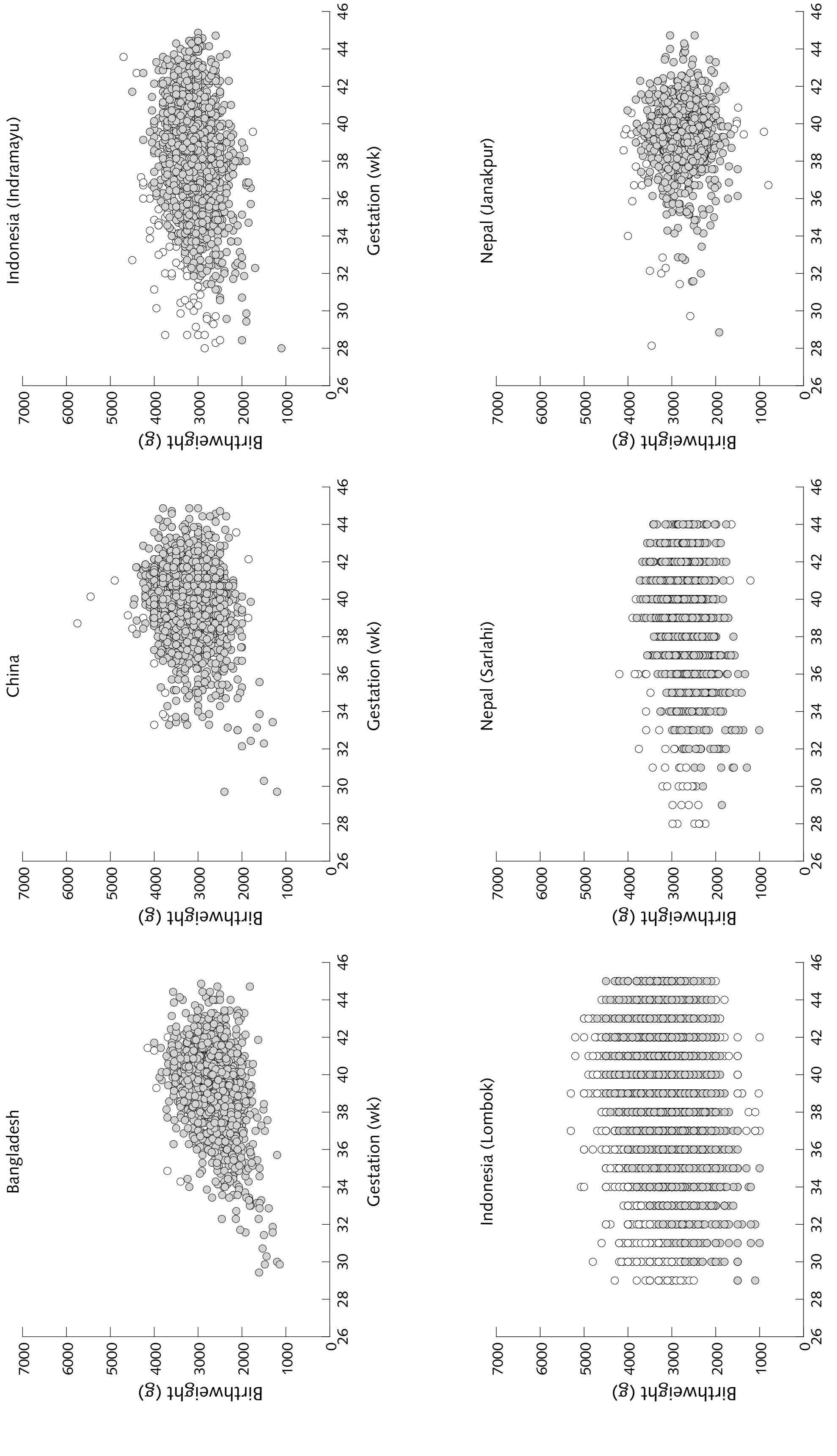
Birthweight

Results for birthweight and prevalence of LBW, SGA, and LGA births are shown in **table 1** and **figures 2** and **3**. Compared with the control group, multiple micronutrient supplementation was associated with an increase in mean birthweight (pooled estimate: + 22.4 g [95% CI, 8.3 to 36.4 g]; p = .002; range across studies: + 4.9 to + 75.5 g). There were reductions in the incidence of LBW (pooled OR = 0.89 [95% CI, 0.81 to 0.97]; p = .01; range, 0.70 to 1.24) and SGA birth (pooled OR = 0.90 [95% CI, 0.82 to 0.99]; p = .03; range, 0.73 to 1.05). There was an increase in LGA births (pooled OR = 1.13 [95% CI, 1.00 to 1.28]; p = .04). These results were not significantly altered when adjusted for the infant's sex and the mother's age, weight, parity, and education. The size of the effect on birthweight was unrelated to the mean birthweight in each population (**fig. 2**) (p-value for meta-regression slope = .75). There was no significant heterogeneity between studies.

Interactions with maternal characteristics

We examined whether the effects of multiple micronutrients on birthweight varied according to maternal age, parity, BMI, and height. The Indonesia (Indramayu), Nepal (Sarlahi), and Mexico studies showed significant linear interactions with maternal BMI, with a larger effect of multiple micronutrient supplementation on birthweight as maternal BMI increased (**figs. 4** and **5**). Meta-analysis (**fig. 5**) showed an overall difference in effect on birthweight between the multiple micronutrient and control groups of 7.6 g (95% CI, 1.9 to 13.3 g) per kilogram per square meter increase in maternal BMI (p for interaction = .009). There was moderate heterogeneity among studies (I^2 = 36%, p = .10) (**fig. 5**). In some studies, the intervention effect relative to the control group was negative in women with low BMI (**fig. 4**). In a pooled analysis of all studies, the intervention effect relative to the control group was +39.0 g (95% CI, +22.0 to +56.1 g) in mothers with BMI of 20 kg/m^2 or higher, compared with –6.0 g (95% CI, –28.8 to +16.8 g) in mothers with BMI less than 20 kg/m^2, a difference that was highly statistically significant (p < .001) and did not change after adjustment for maternal age and education.

The Guinea-Bissau and Niger studies showed significant interactions with maternal height, with larger effects on birthweight in taller mothers. However, this effect was inconsistent between studies, and there was no significant overall effect (the difference in the effect on birthweight between multiple micronutrient supplementation and iron–folic acid supplementation was + 1.4 g per centimeter increase in maternal height; p for interaction = .18). The Burkina Faso study showed a positive effect of the intervention with multiple micronutrients on birthweight in multiparous mothers, but no effect in nulliparous mothers. The opposite was true in the Nepal (Janakpur) and Pakistan studies. In a pooled analysis, there was no significant interaction with parity, regardless of how the data were categorized (p for interaction = 0.7 using parity as a binary variable, nulliparous versus multiparous). There was


Indonesia (Indramayu)
China
Bangladesh
Nepal (Janakpur)
Nepal (Sarlahi)
Indonesia (Lombok)
Birthweight (g)
Gestation (wk)
0
1000
2000
3000
4000
5000
6000
7000
26
28
30
32
34
36
38
40
42
44
46

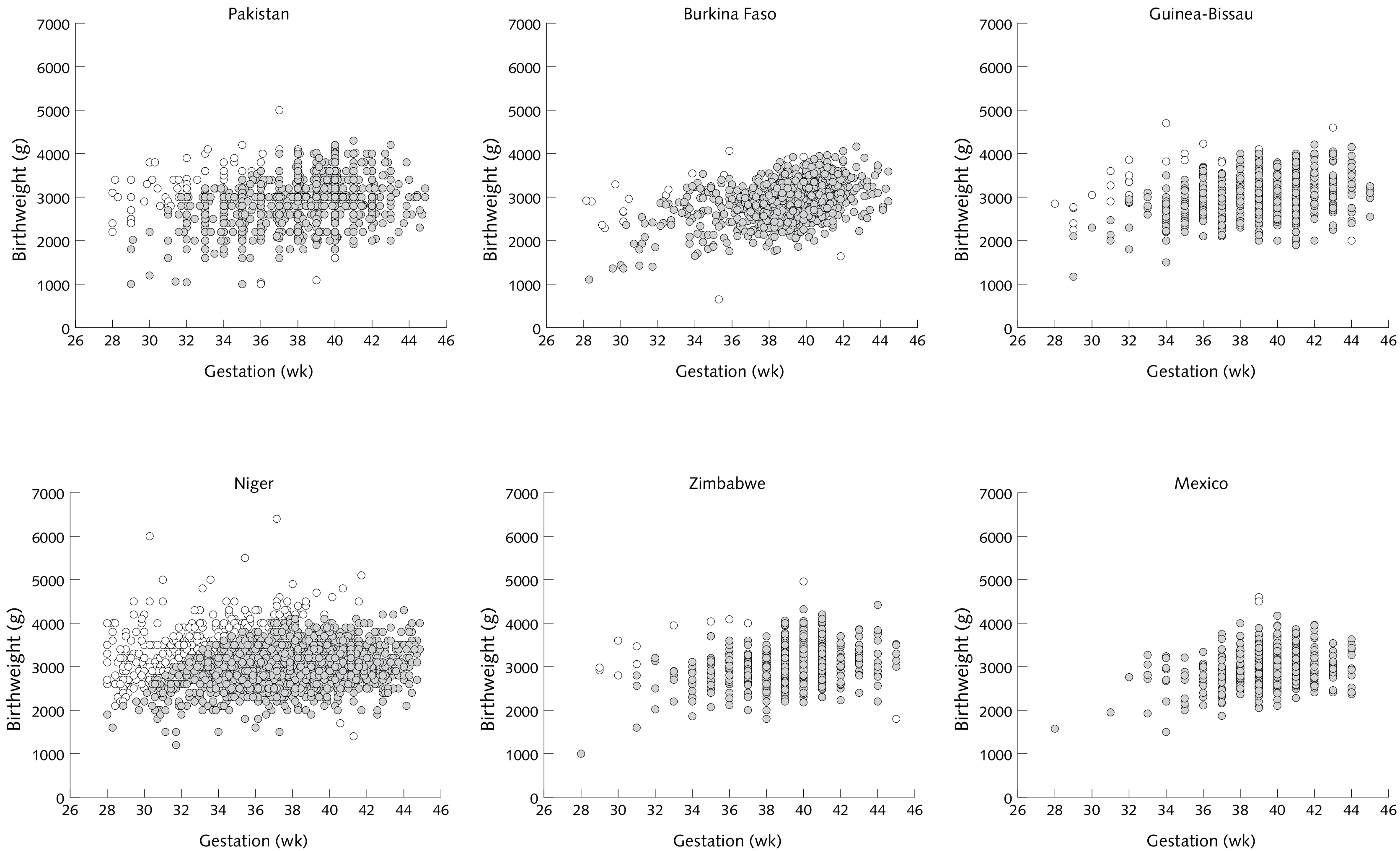


FIG. 1. Scatterplots of birthweight according to gestational age, for each of the 12 trials, showing (open circles) data removed because of implausible combinations of birthweight and gestational age (all based on the "restricted sample")

TABLE 1. Birth outcomes in multiple micronutrient and control groups[a]

Study	Mean ± SD birthweight (g) MMN	Mean ± SD birthweight (g) Control	LBW (< 2,500 g) (%) MMN	LBW (< 2,500 g) (%) Control	SGA (within-cohort < 10th centile) (%) MMN	SGA (within-cohort < 10th centile) (%) Control	LGA (within-cohort > 90th centile) (%) MMN	LGA (within-cohort > 90th centile) (%) Control	Mean ± SD gestation (days) MMN	Mean ± SD gestation (days) Control	Preterm birth (< 37 wk) (%) MMN	Preterm birth (< 37 wk) (%) Control
Bangladesh [10]	2,654 ± 399 *n* = 904	2,643 ± 427 *n* = 914	32.3 *n* = 904	35.7 *n* = 914	9.5 *n* = 901	10.5 *n* = 910	9.1 *n* = 901	10.9 *n* = 910	275 ± 14 *n* = 901	274 ± 15 *n* = 910	9.8 *n* = 901	12.7 *n* = 910
China [11]	3,208 ± 428 *n* = 1,364	3,189 ± 415 *n* = 1,418	3.3 *n* = 1,364	3.7 *n* = 1,418	9.6 *n* = 1,352	10.4 *n* = 1,415	10.2 *n* = 1,352	9.8 *n* = 1,415	279 ± 12 *n* = 1,352	279 ± 12 *n* = 1,415	4.1 *n* = 1,352	4.7 *n* = 1,415
Indonesia (Indramayu) [12]	3,086 ± 436 *n* = 726	3,081 ± 416 *n* = 709	6.9 *n* = 726	5.6 *n* = 709	9.4 *n* = 692	10.7 *n* = 676	11.1 *n* = 692	8.7 *n* = 676	269 ± 20 *n* = 692	270 ± 19 *n* = 676	27.9 *n* = 692	25.7 *n* = 676
Indonesia (Lombok) [13]	3,188 ± 485 *n* = 6,791	3,171 ± 490 *n* = 6,479	4.6 *n* = 6,791	5.3 *n* = 6,479	9.9 *n* = 6,492	10.2 *n* = 6,177	10.1 *n* = 6,492	9.7 *n* = 6,177	273 ± 19 *n* = 6,492	273 ± 19 *n* = 6,177	21.7 *n* = 6,492	21.0 *n* = 6,177
Nepal (Sarlahi) [14]	2,667 ± 432 *n* = 676	2,659 ± 429 *n* = 611	34.5 *n* = 676	33.2 *n* = 611	10.2 *n* = 648	9.8 *n* = 589	9.6 *n* = 648	10.4 *n* = 589	272 ± 18 *n* = 648	270 ± 19 *n* = 589	17.9 *n* = 648	21.1 *n* = 589
Nepal (Janakpur) [15]	2,809 ± 446 *n* = 500	2,733 ± 426 *n* = 496	19.2 *n* = 500	25.4 *n* = 496	8.8 *n* = 480	11.4 *n* = 483	12.5 *n* = 480	7.5 *n* = 483	275 ± 13 *n* = 480	276 ± 12 *n* = 483	8.1 *n* = 480	7.5 *n* = 483
Pakistan [16]	2,928 ± 568 *n* = 413	2,853 ± 521 *n* = 488	18.9 *n* = 413	21.1 *n* = 488	8.6 *n* = 372	11.4 *n* = 456	12.1 *n* = 372	8.1 *n* = 456	266 ± 20 *n* = 372	266 ± 21 *n* = 456	29.6 *n* = 372	29.4 *n* = 456
Burkina Faso [17]	2,919 ± 442 *n* = 493	2,889 ± 418 *n* = 494	14.6 *n* = 493	15.8 *n* = 494	9.8 *n* = 481	10.2 *n* = 488	10.6 *n* = 481	9.2 *n* = 488	273 ± 16 *n* = 481	274 ± 16 *n* = 488	13.9 *n* = 481	13.1 *n* = 488
Guinea-Bissau [18]	3,063 ± 524 *n* = 294	3,014 ± 460 *n* = 306	11.9 *n* = 294	12.7 *n* = 306	8.6 *n* = 279	11.3 *n* = 291	12.2 *n* = 279	7.9 *n* = 291	274 ± 21 *n* = 279	274 ± 20 *n* = 291	23.2 *n* = 279	22.3 *n* = 291
Niger [19]	3,106 ± 492 *n* = 1,214	3,033 ± 466 *n* = 1,107	6.9 *n* = 1,214	7.9 *n* = 1,107	9.1 *n* = 1,039	11.1 *n* = 937	10.9 *n* = 1,039	9.0 *n* = 937	263 ± 21 *n* = 1,039	264 ± 21 *n* = 937	41.9 *n* = 1,039	40.9 *n* = 937
Zimbabwe [20]	3,084 ± 430 *n* = 341	3,052 ± 426 *n* = 355	6.5 *n* = 341	9.0 *n* = 355	8.9 *n* = 325	11.1 *n* = 334	11.1 *n* = 325	8.6 *n* = 334	276 ± 15 *n* = 325	274 ± 17 *n* = 334	11.1 *n* = 325	14.7 *n* = 334
Mexico [21]	2,990 ± 380 *n* = 297	2,981 ± 403 *n* = 286	7.7 *n* = 297	8.7 *n* = 286	9.1 *n* = 296	11.0 *n* = 283	10.1 *n* = 296	9.5 *n* = 283	277 ± 14 *n* = 296	277 ± 15 *n* = 283	7.1 *n* = 296	6.4 *n* = 283
Pooled effect	+ 22.4 g 95% CI, 8.3 to 36.4 g *p* = .002		OR = 0.89 95% CI, 0.81 to 0.97 *p* = .01		OR = 0.90 95% CI, 0.82 to 0.99 *p* = .03		OR = 1.13 95% CI, 1.00 to 1.28 *p* = .04		0.17 days 95% CI, − 0.35 to +0.70 *p* = .51		OR = 1.00 95% CI, 0.93 to 1.09 *p* = .9	
Pooled adjusted effect	+ 22.5 g 95% CI, 8.1 to 36.9 g *p* = .002		OR = 0.88 95% CI, 0.80 to 0.97 *p* = .01		OR = 0.90 95% CI, 0.82 to 0.99 *p* = .04		OR = 1.15 95% CI, 0.99 to 1.34 *p* = .06		0.11 days 95% CI, − 0.45 to + 0.68 *p* = .70		OR = 1.02 95% CI, 0.94 to 1.11 *p* = .7	

CI, confidence interval; LBW, low-birthweight; LGA, large-for-gestational age; MMN, multiple micronutrients; OR, odds ratio; SGA, small-for-gestational age

a. The following were excluded: women known to be HIV-positive, women known to have a multiple pregnancy, fetal losses before 28 weeks, stillbirths, infants with gestational age at delivery < 189 or > 314 days, and babies measured > 72 hours after birth. Only one pregnancy (the earliest) was included for each mother. Information on the age at which the baby was measured was not available for Burkina Faso, Zimbabwe, and Mexico. For outcomes including gestation (SGA, LGA, length of gestation, and preterm birth), women were excluded from the analysis if the gestational age was unlikely given the birthweight (see Statistical Methods). The pooled estimates are derived from random-effects meta-analysis, with adjustment for cluster design in six of the studies. Adjusted effects are further adjusted for maternal age and weight at recruitment, parity, and education and the sex of the baby.

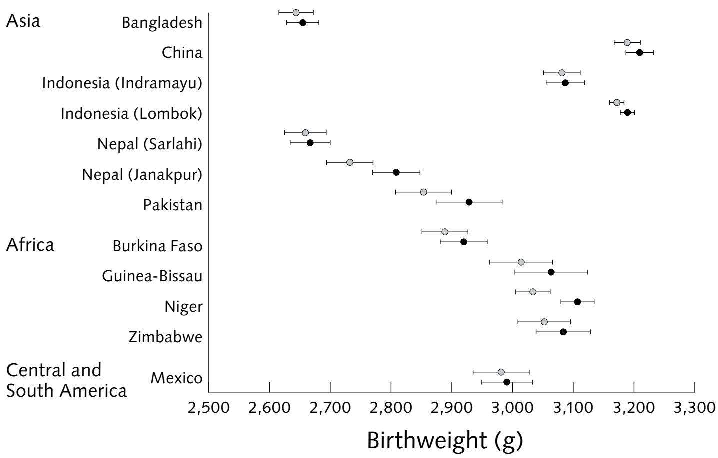


FIG. 2. Mean (95% CI) birthweight for multiple micronutrient (filled circles) and control (open circles) groups in each center

no significant interaction between supplement type and maternal age.

Other birth measurements

Birth length was available in all 12 studies except Indonesia (Lombok). There were no significant effects of micronutrient supplementation on birth length in any individual study (range, −0.2 to +0.7 cm), and there was no significant effect in the meta-analysis (pooled estimate, +0.06 cm; $p = .20$). Head circumference was measured in 10 studies (not in Bangladesh or Mexico). The mean effect of multiple micronutrient supplementation ranged from −0.4 to +0.3 cm. The meta-analysis showed no overall effect (pooled estimate, +0.03 cm; $p = .47$). Mid-upper-arm circumference was measured in three studies (Pakistan, Burkina Faso, and Guinea-Bissau). The effect of multiple micronutrient supplementation ranged from +0.1 to +0.8 cm. The meta-analysis showed no overall effect (pooled estimate, +0.6 cm; $p = .16$).

Duration of gestation and preterm births

The intervention with multiple micronutrients was not associated with an increase in gestation (pooled effect, +0.17 days [95% CI, −0.35 to +0.70]; $p = .51$; range, −0.76 to +2.2 days) or a reduction in preterm births (pooled OR = 1.00 [95% CI, 0.93 to 1.09]; $p = .92$; range, 0.72 to 1.13) (**table 1** and **fig. 3**).

Duration of supplementation

There was no evidence that starting supplements earlier in pregnancy was associated with greater effects (data not shown).

Fully adjusted analyses

The findings for all outcomes were little changed if we adjusted for maternal weight, age, parity, and education and infant's sex (see pooled adjusted estimates in **table 1**). The findings were similar if the raw data were used and if subjects with implausible gestational ages were retained, and there were no changes in the main findings if the Mexico trial, in which the control group received iron alone, was excluded.

Discussion

We had the privilege of access to the raw data from 12 recent, high-quality, randomized, controlled trials, all carried out with similar protocols in low-income countries. All used a multiple micronutrient supplement providing approximately 1 RDA of an extensive range of vitamins and minerals (nine used an identical multiple micronutrient supplement, UNIMMAP [United Nations International Multiple Micronutrient Preparation]). Overall, multiple micronutrient supplementation led to a significant, although small, increase (22.4 g) in birthweight, reductions in LBW and SGA births (11% and 10%, respectively), and an increase (13%) in LGA births, compared with iron–folic acid (nine trials), iron–folic acid and vitamin A (one trial), iron alone (one trial), or placebo (one trial). There were no significant increases in other birth measurements (length, head circumference, and mid-upper-arm circumference), although data on mid-upper-arm circumference were limited. There was a consistent lack of effect on the duration of gestation or the incidence of preterm delivery. The effect of multiple micronutrient supplementation on birthweight therefore appears to be due mainly to an increase in size for gestational age (indicating more rapid fetal growth) and to increased

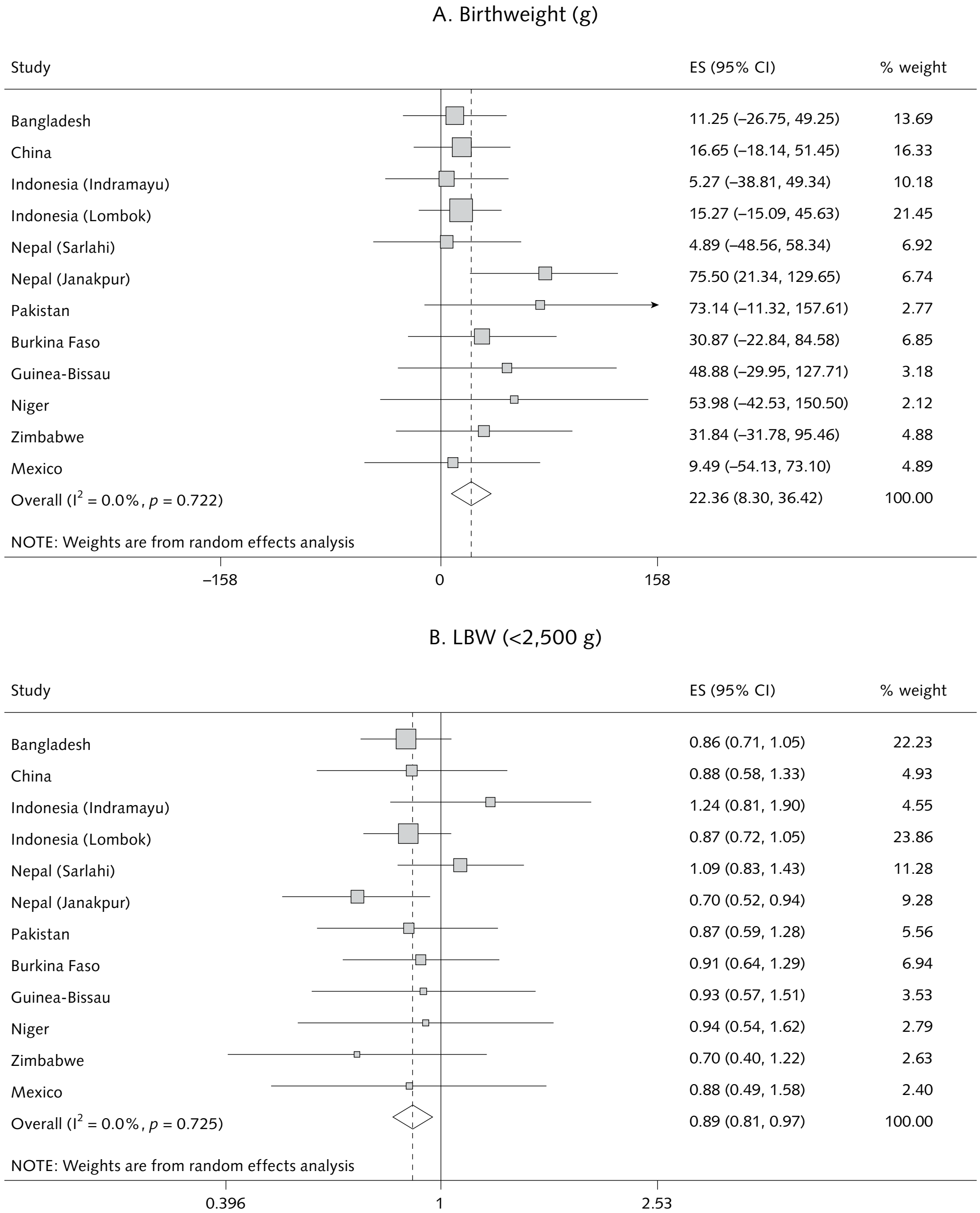


FIG. 3. Random-effects model forest plots for effects of MMN supplementation compared with controls on (a) birthweight, (b) low birthweight, (c) SGA births, (d) LGA births, (e) gestation and (f) pre-term delivery

soft tissue rather than skeletal growth and to be manifested by an upward shift in the entire birthweight distribution. The effect on birthweight of multiple micronutrient supplementation was most strongly positive in mothers with higher BMI. In mothers with low BMI, the effect of multiple micronutrients relative to the control group was close to zero in most studies and was negative in some studies (**fig. 4**).

The increase in birthweight and reduction in LBW and SGA births was consistent with the results of an earlier meta-analysis [9] and with other, more recent trials [29, 30]. There was no increase in other birth measurements. The Burkina Faso trial reported a 2.9-mm increase in birth length [17], but there was no significant effect in the subset of pregnancies included in this meta-analysis, and none of the other original trials reported an increase in birth length. There was no reduction in preterm births. This conclusion seems robust, because although gestational age was clearly inaccurately estimated in some studies (**fig. 1**), there was no effect of multiple micronutrient supplementation on gestation or incidence of preterm delivery, even

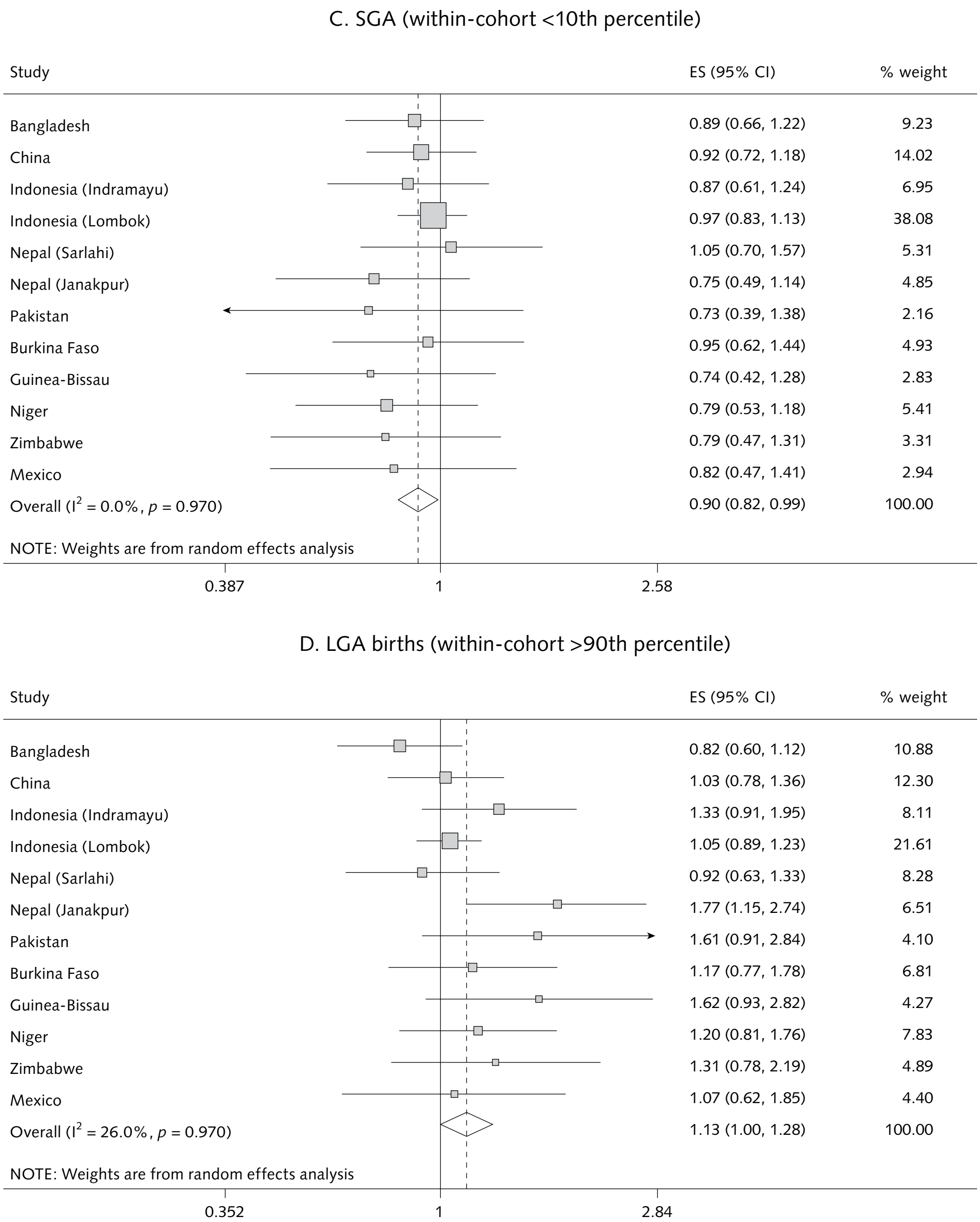


FIG. 3 *(continued)*. Random-effects model forest plots for effects of MMN supplementation compared with controls on (a) birthweight, (b) low birthweight, (c) SGA births, (d) LGA births, (e) gestation and (f) preterm delivery

in the studies in which very few babies were excluded because of implausible associations between birthweight and gestation.

An important question is whether the small overall increase in birthweight translates into functional benefits for the children. Based on the relationship of birthweight to infant mortality [28], an increase of 22.4 g would be expected to result in a negligible reduction in infant mortality. Only 1 of the 12 trials (Lombok, Indonesia) [13] was powered to examine this outcome, and this trial showed a reduction in infant mortality. However, a meta-analysis in this issue by Ronsmans et al. of infant mortality in the 12 trials [31] showed no reduction in stillbirths, perinatal mortality, or early and late neonatal mortality. There are now some published studies of other functional outcomes in the children born in these trials. The Nepal (Sarlahi) group found no benefits of multiple micronutrient supplementation on morbidity in infancy [32]. However, the Nepal (Janakpur) study group recently reported

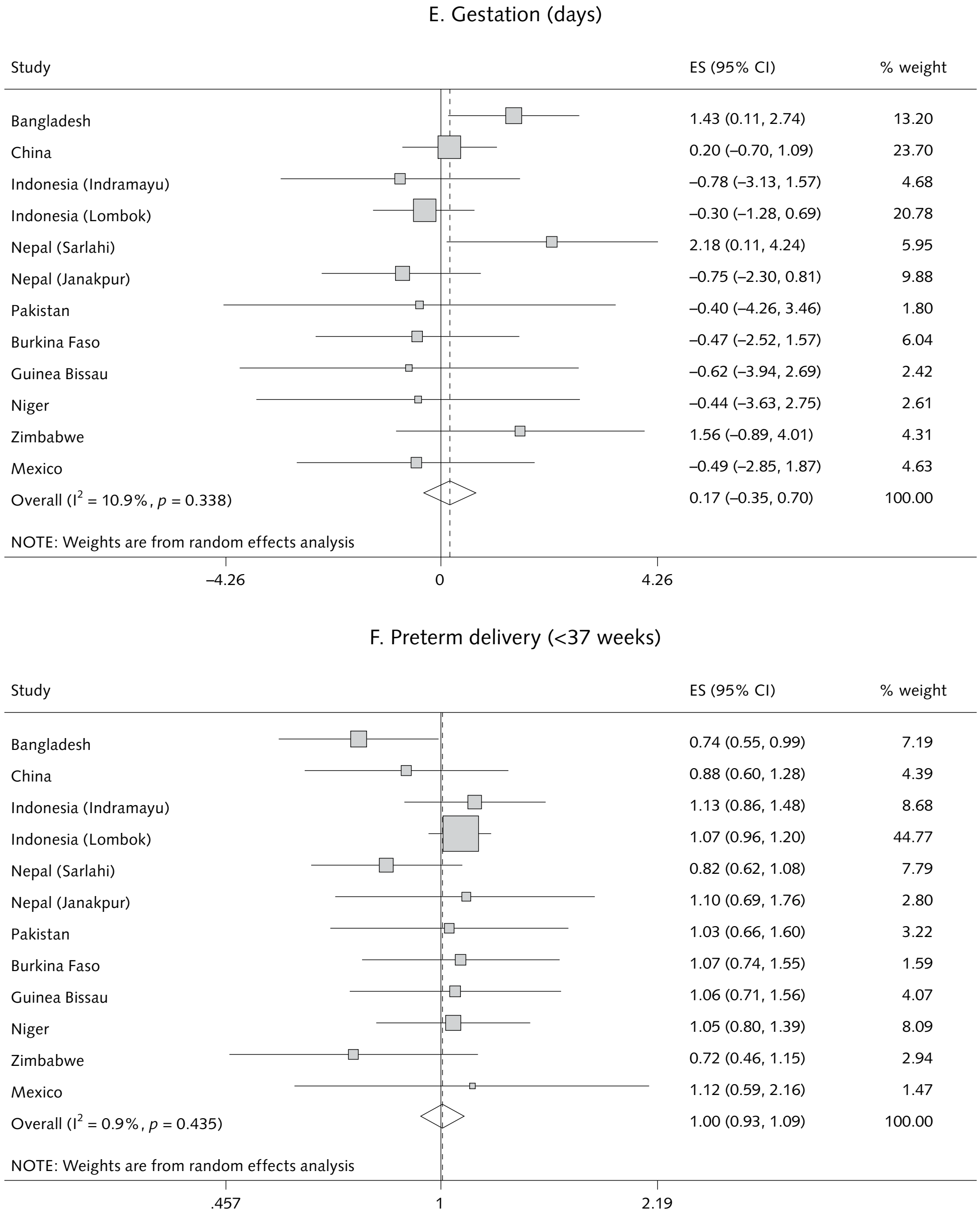


FIG. 3 *(continued)*. Random-effects model forest plots for effects of MMN supplementation compared with controls on (a) birthweight, (b) low birthweight, (c) SGA births, (d) LGA births, (e) gestation and (f) preterm delivery

that at 2.5 years, children of mothers who had taken multiple micronutrient supplements were on average 200 g heavier than control children, had larger head, chest, and mid-upper-arm circumferences and triceps skinfold thickness, and lower systolic blood pressure [33]. More such follow-up studies are needed in order to weigh up the potential public health benefits of multiple micronutrient supplementation. Effects on the well-being of the mother also need to be included in the assessment of benefits; the paper by Allen and Peerson in this issue [34] showed that multiple micronutrient supplementation improved maternal hemoglobin and micronutrient status.

We found that multiple micronutrient supplementation was associated with an increase in the incidence of LGA babies (defined as above the 90th within-population percentile) as well as a reduction in the incidence of SGA babies. In debates about nutritional interventions in malnourished women, concern has been expressed about the possibility of inducing

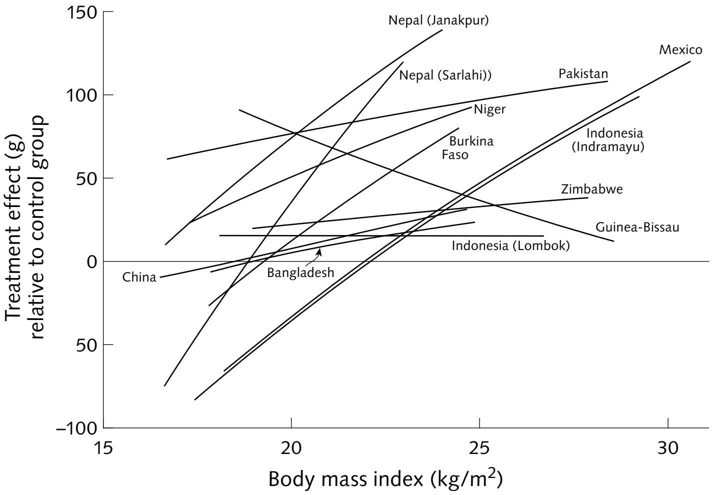


FIG. 4: Effect on birthweight of MMN supplementation relative to the control group according to maternal BMI. The lines are truncated to the 5th and 95th percentiles for BMI for each dataset

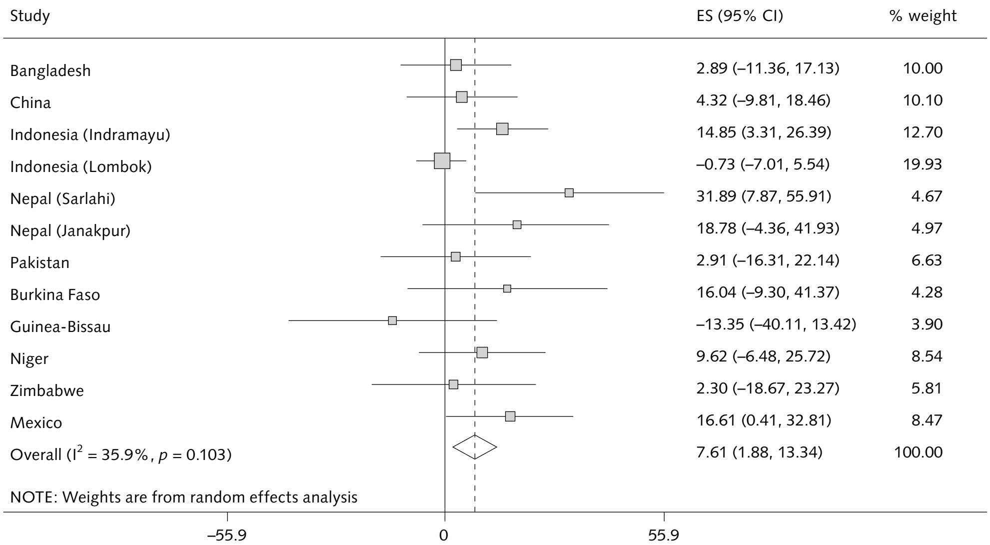


FIG. 5: Random effects model showing the interaction between maternal BMI and supplement effect. The effect size indicates the change in birthweight (g) in the MMN group relative to the control groups per unit increase in maternal BMI

cephalopelvic disproportion and thus increasing the number of obstructed deliveries [35]. Against this is the argument that interventions would have their maximal effect at the lower end of the birthweight range and would prevent LBW but not produce an increase in the number of large babies [36]. Our analysis showed that multiple micronutrient supplementation produced an upward shift of the whole birthweight distribution. The Nepal (Sarlahi) study group has carried out a detailed analysis of the birthweight distribution in the different arms of their trial [37]. Multiple micronutrient supplementation increased birthweight across the whole distribution, in contrast to the other interventions (folic acid, iron–folic acid, and iron–folic acid–zinc), which specifically reduced the number of babies in the lower tail of the distribution. The authors suggested that reporting the change in mean birthweight is not a sufficient description of the effects of an intervention. They argued that interventions acting mainly at the lower end of the distribution may be preferable to those that produce a rightward shift of the whole distribution, and that the latter may even be harmful and could explain the (nonstatistically significant) increases in birth asphyxia and neonatal mortality in the group receiving multiple micronutrients in their study [37–39]. Head size is the neonatal measurement most likely to influence the risk of cephalopelvic disproportion. In our analysis, there was no significant effect of multiple micronutrient supplementation on newborn head circumference. However, the duration of labor and the incidence of assisted or operative delivery were not included in our analysis, and it would be important to consider these outcomes in further work. Data on these outcomes were not included in most of the publications from these 12 trials.

The positive effect of multiple micronutrient supplementation on birthweight was greatest in heavier women (**fig. 4**). The corollary of this was that the mean effect on birthweight among women with low BMI was around zero for most studies. The trials were not designed to examine interactions with maternal size, and these post hoc analyses must therefore be treated with caution [40, 41]. However, it is reasonable to speculate that micronutrients are not optimally utilized in the presence of maternal energy deficiency and may conceivably place additional strain on energy-deficient mothers because of the need to metabolize them.

We suggest that better evidence of functional benefits for mothers and children is required before multiple micronutrients can be recommended on a large scale in place of iron–folic acid. The data on infant mortality presented by Ronsmans et al. in this issue [31] suggest that further research and monitoring in studies with larger sample sizes are required. We included in our meta-analysis only studies that provided approximately 1 RDA of multiple micronutrients. The Guinea-Bissau trial included in this review had a 2× RDA group, and the increase in birthweight was larger than in the 1× RDA group [18]. Another study in Tanzania, using supplements containing twice the RDA of micronutrients, in HIV-positive mothers, also showed a large effect on birthweight and a 44% reduction in LBW [42]. However, a 2× RDA supplement for HIV-negative women in the same setting [43] did not suggest any greater benefit. There is evidence from animal studies that improvements in maternal nutrition require more than one generation to produce improvements in fetal growth [44]. In the Guatemala INCAP trial, maternal supplementation with Atole (a high-energy, high-protein, multiple micronutrient supplement) had no significant effect on birthweight compared with Fresco (a supplement containing the same micronutrients but less energy and no protein), but the children grew taller [45]. This should produce improved birth outcomes in the next generation [46]. Such long-term follow-up will be needed to establish the full effects of nutritional interventions in mothers. It is important that the trials included in our analysis be utilized to their full potential in this way.

There is already good evidence that micronutrient supplementation *before conception* has benefits for fetal development. The best example is periconceptional folic acid supplementation, which reduces the incidence of neural tube defects [47]. Supplementation of women only after they know that they are pregnant is therefore clearly a less than optimal intervention. Furthermore, there is growing evidence that maternal undernutrition in the periconceptional period increases the risk of preterm delivery [48, 49] and reduces fetal growth, even if nutrition improves later in pregnancy. Future research should include studies of maternal nutrient repletion before as well as during pregnancy.

In conclusion, supplementation of pregnant women with 1 RDA of multiple micronutrients increases birthweight and substantially reduces the rates of LBW and SGA births. The effect on birthweight is greater in women with higher BMI and is very small in energy-deficient mothers. There appears to be an upward shift of the whole birthweight distribution, resulting in an increase in LGA births. Further research is needed to assess the effects of these changes in fetal growth on future health and capacity.

Acknowledgments

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Multiple micronutrient supplementation during pregnancy in low-income countries: A meta-analysis of effects on stillbirths and on early and late neonatal mortality

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Abstract

Background. *Multiple micronutrient deficiencies are common among women in low-income countries and may adversely affect pregnancy outcomes*

Objective. *To conduct a meta-analysis of the effects on stillbirths and on early and late neonatal mortality of supplementation during pregnancy with multiple micronutrients compared with iron–folic acid in recent randomized, controlled trials.*

Methods. *Twelve randomized, controlled trials were included in the analysis (Bangladesh; Burkina Faso; China; Guinea-Bissau; Indramayu and Lombok, Indonesia; Mexico; Sarlahi and Janakur, Nepal; Niger; Pakistan; and Zimbabwe), all providing approximately 1 recommended dietary allowance (RDA) of multiple micronutrients or iron–folic acid to presumed HIV-negative women.*

Results. *Supplementation providing approximately 1 RDA of multiple micronutrients did not decrease the risk of stillbirth (OR = 1.01; 95% CI, 0.88 to 1.16), early neonatal mortality (OR = 1.23; 95% CI, 0.95 to 1.59), late neonatal mortality (OR = 0.94; 95% CI, 0.73 to 1.23), or perinatal mortality (OR = 1.11; 95% CI, 0.93 to 1.33).*

Conclusions. *Our meta-analysis provides consistent evidence that supplementation providing approximately 1 RDA of multiple micronutrients during pregnancy does not result in any reduction in stillbirths or in early or late neonatal deaths compared with iron–folic acid alone.*

Introduction

The World Health Organization (WHO) recommends universal distribution of iron–folic acid supplements to all pregnant women in developing countries [1]. Because many women face additional micronutrient deficits, particularly during pregnancy, repletion of pregnant women with minerals and vitamins has been suggested as a way to further improve birth outcomes in countries with a high burden of undernutrition [2]. Daily multiple micronutrients during pregnancy have been shown to reduce the number of low-birthweight (LBW) and small-for-gestational-age (SGA) babies and the incidence of maternal anemia [3]. A recent meta-analysis of multiple micronutrient supplementation during pregnancy reported a small, statistically significant increase in birthweight when compared with iron–folic acid supplementation, but there was no effect on the incidence of preterm birth [4]. Another meta-analysis showed reductions in anemia and iron deficiency and several other micronutrient deficiencies with the use of multiple micronutrients [5].

If multiple micronutrients affect fetal growth, particularly SGA births [6], a direct beneficial effect on perinatal or neonatal survival can be hypothesized. A systematic review of nine trials did not find a significant difference in perinatal mortality when multiple micronutrient supplementation was compared with supplementation with one or two micronutrients, iron–folic acid supplementation, no supplementation, or placebo [3]. However, two trials in Nepal reported

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nonsignificant increases in perinatal and neonatal deaths associated with multiple micronutrient supplementation compared with supplementation with iron–folic acid only] [7]. Although these results have been called into question [8, 9], the possibility of adverse outcomes in relation to multiple micronutrient supplementation certainly warrants further investigation.

At the time of the systematic review conducted by Haider and Bhutta [3], a number of trials of multiple micronutrient supplementation were still ongoing. The present study updates the review and assesses the effect of supplementing pregnant women with a daily multiple micronutrient tablet compared with iron–folic acid on stillbirths, early and late neonatal mortality, and perinatal mortality.

Methods

Search protocol and study review

Details of the search strategy and study review are reported elsewhere [10]. In brief, findings are reported from randomized, controlled trials supplementing pregnant women with daily multiple micronutrients. For studies with more than one intervention or control arm, only one comparison group was selected [10]. **Table 1** lists the 12 trials included in this review. In brief, nine studies [6, 11–14, 16–19] used the UNICEF/United Nations University/World Health Organization-recommended daily composition of the multiple micronutrient tablet UNIMMAP (United Nations International Multiple Micronutrient Preparation), while the studies in Mexico [21], Nepal (Sarlahi) [15], and Zimbabwe [20] used slightly different preparations. UNIMMAP contains 30 mg of iron, 15 mg of zinc, 2 mg of copper, 65 µg of selenium, 150 µg of iodine, 800 µg RE of vitamin A, 1.4 mg of vitamin B_1, 1.4 mg of vitamin B_2, 400 µg of folic acid, 18 mg of niacin, 1.9 mg of vitamin B_6, 2.6 µg of vitamin B_{12}, 70 mg of vitamin C, 200 IU of vitamin D, and 10 mg of vitamin E. The studies in Nepal (Sarlahi) and Mexico used multiple micronutrients containing 60 mg of iron, and in Zimbabwe iron–folic acid was not included in the multiple micronutrients but was supplied separately as part of routine antenatal care.

The control regimen consisted of 60 mg of iron and 400 µg of folic acid, except for the studies in Indonesia (Lombok) and Bangladesh, which used 30 mg of iron. Women in Zimbabwe received the routine antenatal prescription of iron–folic acid. Six trials were cluster randomized and six used individual randomization.

Statistical methods

From the selected studies, data were extracted on the number of live births and stillbirths and on early and late neonatal mortality. The coding of data on fetal loss, stillbirths, and live births was accepted from that reported in the data for each study. A stillbirth was defined as the death of a fetus after 28 weeks or more of gestation but before delivery of the baby's head, which is consistent with the definition generally used in developing countries. Early neonatal death was defined as death of a live-born infant within 7 completed days after birth. Late neonatal death was defined as death of an infant between 8 and 28 completed days after birth. Data on stillbirths and early neonatal deaths were also pooled as perinatal deaths, because early neonatal deaths may be wrongly registered as stillbirths [22]. The denominators for the rates of stillbirth, early neonatal death, late neonatal death, and perinatal death are all births (live births and stillbirths), all live births, all neonates surviving after the first week, and all births, respectively. Women were excluded from the analysis if they were known to be HIV positive, if they had multiple pregnancies or fetal loss, or if it was not known whether their infant was born dead or alive. Only one pregnancy was included for each woman.

Statistical analyses and meta-analyses were performed with the use of Stata 10. The overall effect of multiple micronutrient supplementation on the risk of stillbirth, early neonatal death, perinatal death, and late neonatal death was assessed. Crude mortality rates in intervention and control arms, with 95% confidence intervals adjusted for clustering where appropriate, were also reported. Odds ratios with 95% confidence intervals were used as a measure of the effect of multiple micronutrient supplementation on mortality. Random-effects models were used to calculate the pooled odds ratio for multiple micronutrient supplementation compared with controls, with adjustment for cluster design where appropriate. The results were presented based on analyses using random-effects models because of the differences between the study populations in level of mortality, intervention and control regimens, duration of intervention, and dietary intake. Heterogeneity between studies was measured by the *I*-square statistic and was tested for significance by using a chi-square test on the *Q* statistic. Because the review was heavily weighted toward the large Indonesia (Lombok) study [14], an a priori sensitivity analysis was performed by removing this study from the meta-analysis.

Results

Levels of mortality

There were marked differences between studies in the rates of stillbirth, early neonatal death, and late neonatal death (**table 2** and **figs. 1–3**). Stillbirth rates in the control arm ranged from 5.6 per 1,000 births in

TABLE 1. Characteristics of study populations included in the meta-analyses of data on stillbirths, early and late neonatal mortality, and perinatal mortality[a]

Study	MMN	Control	Cluster or individual randomization	No. of pregnancies	Median (IQR) no. of days since last LMP at start of supplementation	1st pregnancy—%	Mean ± SD maternal height—cm	Maternal baseline BMI < 18.5 kg/m²—%
Bangladesh [11]	UNIMAPP	Iron 30 mg Folic acid 400 µg	Individual	2,412	101 (95–108)	33.7	149.8 ± 5.5	28.5
China [12]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Cluster	3,037	94 (66–126)	64.2	158.8 ± 5.2	10.7
Indonesia (Indramayu) [13]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Cluster	1,598	101 (91–111)	40.8	151.4 ± 5.1	11.4
Indonesia (Lombok) [14]	UNIMAPP	Iron 30 mg Folic acid 400 µg	Cluster	28,643	142 (91–111)	38.8	149.9 ± 4.9	8.3
Nepal (Sarlahi) [15]	Other	Iron 60 mg Folic acid 400 µg Vitamin A	Cluster	1,699	70 (56–91)	26.2	150.1 ± 5.4	30.6
Nepal (Janakpur) [6]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Individual	1,139	114 (102–128)	47.6	150.8 ± 5.7	27.9
Pakistan [16]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Cluster	1,711	98 (81–117)	19.3	152.9 ± 5.9	20.4
Burkina Faso [17]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Individual	1,211	126 (79–166)	21.5	162.2 ± 5.9	11.0
Guinea–Bissau [18]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Individual	1,091	157 (124–190)	31.4	160.5 ± 5.8	5.5
Niger [19]	UNIMAPP	Iron 60 mg Folic acid 400 µg	Cluster	2,896	77 (56–84)	19.5	158.0 ± 6.0	16.9
Zimbabwe [20]	Other	Routine antenatal iron and folic acid supplements	Individual	715	204 (187–223)	47.4	161.5 ± 5.7	3.4
Mexico [21]	Other	Iron 60 mg Folic acid 400 µg	Individual	611	65 (54–79)	64.2	148.7 ± 4.9	6.3

BMI, body mass index; IQR, interquartile range; LMP, last menstrual period; MMN, multiple micronutrients; UNIMAPP, United Nations International Multiple Micronutrient Preparation.

a. Women were excluded who were known to be HIV positive, who were known to have multiple pregnancies, who had fetal loss, or for whom the status of the infant at birth (alive or stillborn) was unknown. Only one pregnancy was included for each woman. The numbers of pregnancies in this table are lower than those reported by Margetts et al. [10] because we excluded women with fetal loss.

Zimbabwe to more than 50 per 1,000 births in Pakistan and Guinea-Bissau. Early neonatal mortality was low in Burkina Faso (5.0 per 1,000 live births) but reached a level of 23.5 per 1,000 live births in Pakistan. Similarly, for late neonatal mortality, the range was between 1.7 deaths per 1,000 children surviving the first week in Burkina Faso to 15.7 deaths per 1,000 in Pakistan.

Effect of multiple micronutrient supplementation on stillbirth, early neonatal mortality, and perinatal mortality

Of the 12 eligible studies, all provided data on stillbirths, and 9 (all but Niger, Zimbabwe, and Mexico) provided data on early neonatal deaths. **Figures 4** to **6** show the results of the meta-analysis for stillbirth and early neonatal and perinatal mortality. With a random-effects model, multiple micronutrient supplementation was not associated with the rate of stillbirth (OR = 1.01; 95% CI, 0.88 to 1.16), but there was a nonsignificant 23% increase in early neonatal mortality (OR = 1.23; 95% CI, 0.96 to 1.59) and a nonsignificant 11% increase in perinatal mortality (OR = 1.11; 95% CI, 0.93 to 1.33). Between-study heterogeneity was moderate for perinatal mortality (I^2 = 46%, p = .07) and early neonatal mortality (I^2 = 34%; p = .15) but low for stillbirths (I^2 = 3%, p = .42). Excluding the large Indonesia (Lombok) study increased all estimates of relative risk. The subsequent odds ratios for stillbirth, early neonatal death, and perinatal death were 1.12 (95% CI, 0.93 to

TABLE 2. Pregnancies, stillbirths, live births, early neonatal deaths, and late neonatal deaths in multiple micronutrient and control groups

Study	No. of pregnancies (no. of stillbirths)		No. of live births (no. of early neonatal deaths)		No. surviving at 1 wk (no. of late neonatal deaths)	
	Control	MMN	Control	MMN	Control	MMN
Bangladesh [11]	1,218 (31)	1,194 (27)	1,187 (20)	1,167 (24)	1,167 (2)	1,143 (5)
China [12]	1,529 (30)	1,508 (39)	1,499 (10)	1,469 (15)	1,489 (6)	1,454 (3)
Indonesia (Indramayu) [13]	792 (13)	806 (13)	779 (18)	793 (14)	761 (3)	779 (2)
Indonesia (Lombok) [14]	14,170 (259)	14,473 (239)	13,911 (241)	14,234 (228)	13,670 (86)	14,006 (81)
Nepal (Sarlahi) [15]	792 (28)	907 (47)	764 (20)	860 (29)	744 (8)	831 (15)
Nepal (Janakpur) [6]	568 (18)	571 (15)	550 (5)	556 (13)	545 (6)	543 (4)
Pakistan [16]	898 (48)	813 (50)	850 (20)	763 (33)	830 (13)	730 (10)
Burkina Faso [17]	604 (9)	607 (15)	595 (3)	592 (5)	592 (1)	587 (2)
Guinea-Bissau [18]	547 (30)	544 (19)	517 (9)	525 (13)	508 (2)	512 (1)
Niger [19]	1,381 (45)	1,515 (57)	—	—	—	—
Zimbabwe [20]	358 (2)	357 (4)	—	—	—	—
Mexico [21]	302 (4)	309 (5)	—	—	—	—

MMN, multiple micronutrients

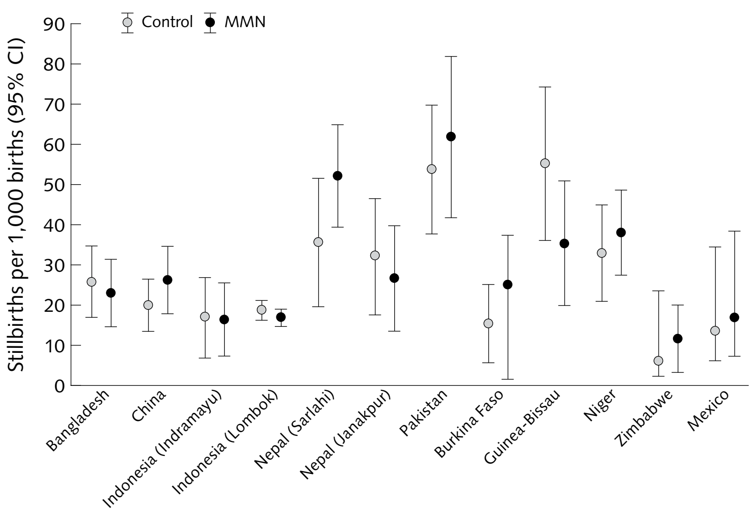

FIG. 1. Stillbirths per 1,000 births in multiple micronutrient (MMN) and control groups

1.34), 1.40 (95% CI, 1.08 to 1.82), and 1.20 (95% CI, 1.01 to 1.42), respectively.

Late neonatal mortality

Data on late neonatal mortality were available for eight studies, which included 22,396 children whose mothers received multiple micronutrient supplementation and 22,003 children in the control arm. The pooled data showed a nonsignificant 6% reduction in late neonatal mortality (OR = 0.94; 95% CI, 0.73 to 1.23) (**fig. 7**). Heterogeneity was low (I^2 = 0%; p = .75) and sensitivity analysis altered the odds ratio slightly (OR = 1.01; 95% CI, 0.64 to 1.60).

Discussion

This meta-analysis provides coherent evidence that multiple micronutrient supplementation does not result in any reduction in the rates of stillbirth or in early or late neonatal death. However, after exclusion of the large Indonesian study from the analysis, the data were consistent with an increase in the risk of

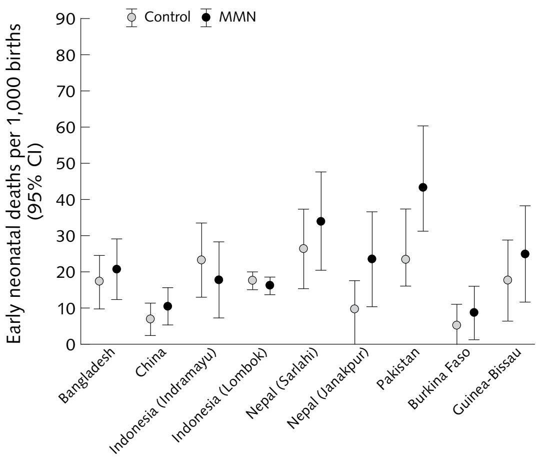

FIG. 2. Early neonatal deaths per 1,000 live births in multiple micronutrient (MMN) and control groups

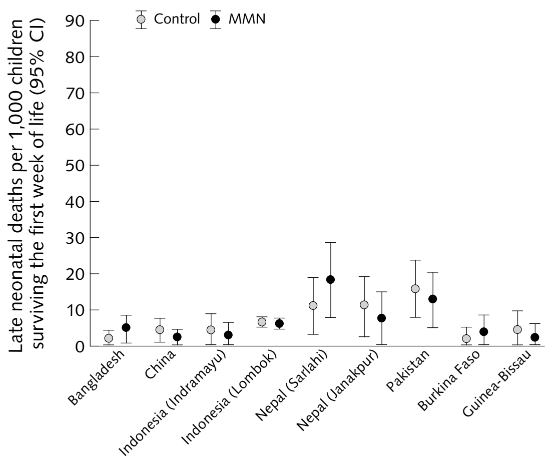

FIG. 3. Late neonatal deaths per 1,000 children surviving the first week of life in multiple micronutrient (MMN) and control groups

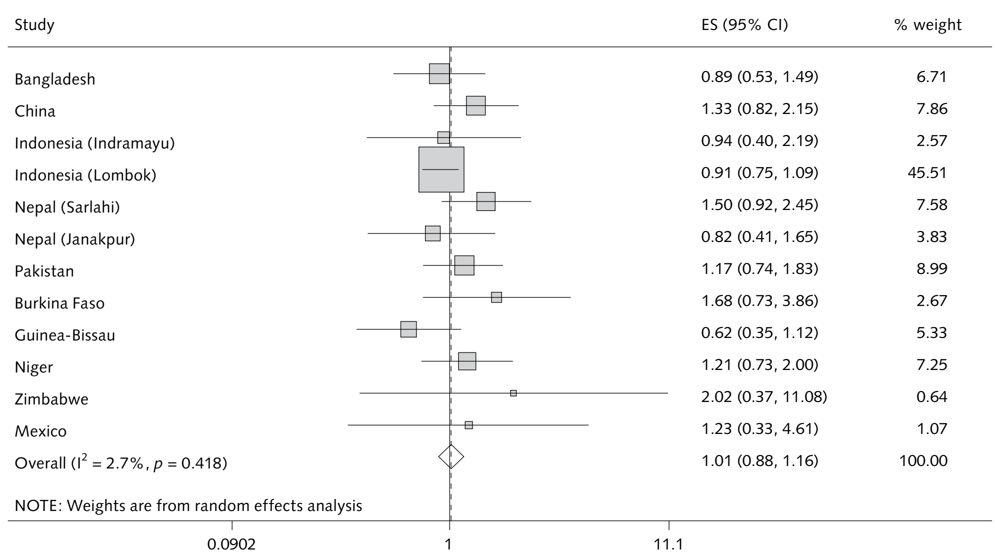

FIG. 4. Random effects model forest plots for effects of multiple micronutrient supplementation on stillbirths. CI, confidence interval; ES, effect size

early neonatal and perinatal mortality in women taking multiple micronutrient supplements during pregnancy compared with those taking iron–folic acid.

The lack of an effect of multiple micronutrient supplements on perinatal or neonatal survival—and the possibility of increased early neonatal and perinatal mortality in women taking multiple micronutrient supplements in some settings—needs to be scrutinized very carefully. This finding is surprising, given that multiple micronutrient supplementation does result in small increases in birthweight [4]. It was expected that there would be a direct beneficial effect on early neonatal and perinatal survival. Increased survival of infants who would otherwise have died *in utero* is unlikely, since multiple micronutrient supplementation was not associated with increased rates of preterm birth [4] or stillbirth. It could be argued that newborns in the control arm had enhanced survival because most mothers in the control arm received higher amounts of iron than those in the group receiving multiple micronutrients. There is no evidence, however, that routine iron supplementation in pregnancy improves health outcomes for babies [23]. Huffman and colleagues [8] suggested that the earlier Nepal findings might be due to a misclassification of stillbirths as neonatal deaths. It was for that reason that perinatal mortality (pooled stillbirths and early neonatal deaths) was assessed, rather than reporting only on neonatal mortality. Increased asphyxia of children born at the upper end of the birthweight distribution [7] may partly explain the adverse effects of multiple micronutrient supplementation on perinatal mortality. In Nepal, children whose mothers had received multiple micronutrients were reported to have a 60% higher risk of birth asphyxia [24].

Meta-analyses have inherent limitations. First, the sample sizes of the trials included in this analysis

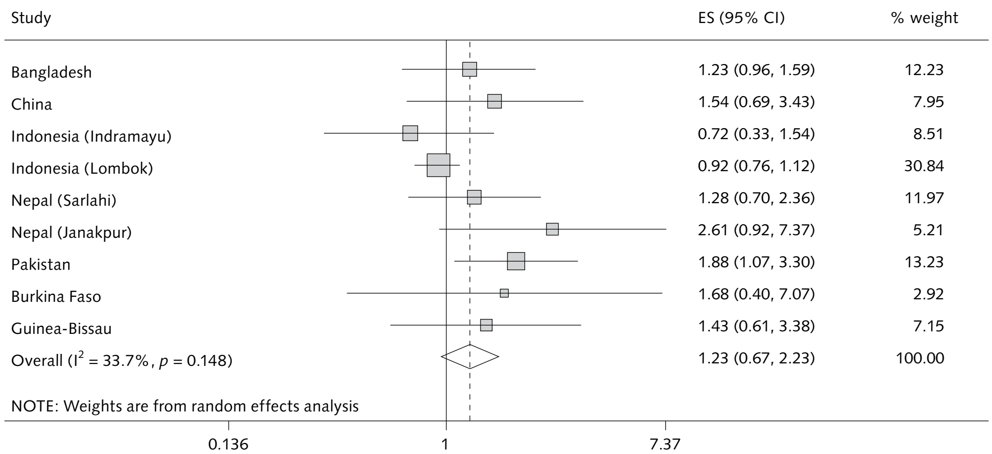

FIG. 5. Random effects model forest plots for effects of multiple micronutrient supplementation on early neonatal deaths. CI, confidence interval; ES, effect size

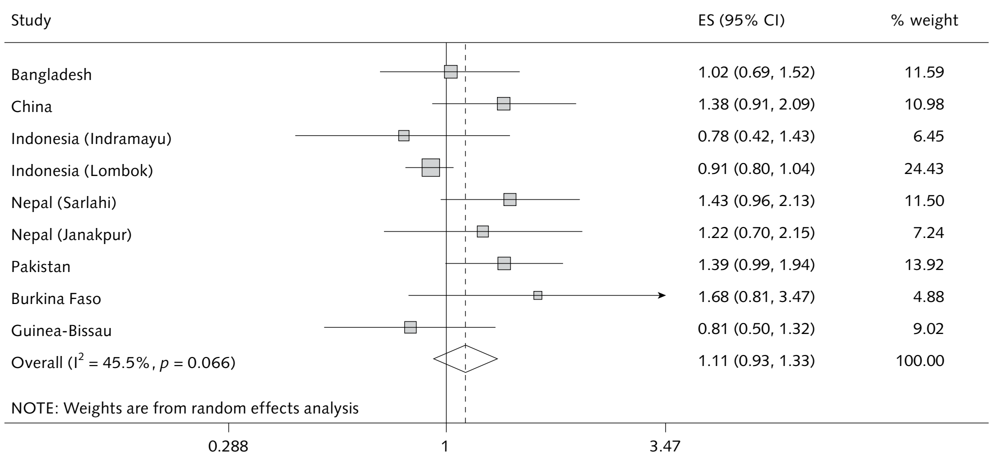

FIG. 6. Random effects model forest plots for effects of multiple micronutrient supplementation on perinatal mortality. CI, confidence interval; ES, effect size

varied, and the results were more likely to be affected by the trials with larger sample sizes. However, the only study powered to examine effects on mortality (the Lombok, Indonesia study) also failed to find a statistically significant effect of multiple micronutrient supplementation on perinatal or neonatal survival [14]. Second, there was significant heterogeneity among studies in perinatal mortality, although the source of this heterogeneity is difficult to ascertain. The study populations differed substantially in terms of nutritional status, reproductive history, and the timing and duration of multiple micronutrient supplementation, all of which may affect the size of the effect of multiple micronutrients on perinatal mortality. The effects of supplements have been found to differ in HIV-infected and -uninfected pregnant women in Tanzania [25], a result suggesting that the burden of infectious diseases may affect nutritional requirements and the size of the effect of multiple micronutrients.

Intervention trials have now expanded the range of endpoints to include neonatal morbidity [24], mortality after the first month of life [14, 26], infant growth and development, and health outcomes later in childhood [27]. In Lombok, Indonesia, early infant mortality after the first month of life was 30% lower in the group receiving multiple micronutrients than in the iron–folic acid group [14]. In Nepal, children whose mothers had taken multiple micronutrients during pregnancy were heavier and of greater body size at the age of 2.5 years than those born to mothers who had received only iron–folic acid [27]. In another study in Nepal, multiple micronutrient supplementation did not improve symptoms of neonatal morbidity, and reported birth asphyxia was higher in the group receiving multiple micronutrients [24]. In the present analysis, data were not available on survival beyond 1 month, and it was not possible to expand the meta-analysis beyond the neonatal period.

It has been suggested that higher doses of multiple micronutrients may be required in malnourished populations [25]. However, the one study that involved a supplement containing twice the RDA of vitamin E and 6 to 10 times the RDAs for several B vitamins and vitamin C in HIV-uninfected pregnant women in Tanzania, and that was powered for effects on fetal death, also found no effect of the supplement on the rate of stillbirth or perinatal mortality [25]. It may be that multiple micronutrient supplementation before conception rather than during pregnancy is the way forward. Periconceptional folic acid supplementation, for example, reduces the incidence of neural tube defects [28], and there is growing evidence that maternal undernutrition in the periconceptional period increases the risk of preterm delivery [29, 30] and reduces fetal growth, even if nutrition improves later in pregnancy. Future research should include studies of maternal nutrient repletion before pregnancy.

What are the implications of our findings for public health? Any suggestion of harm must be carefully weighed against evidence of potential gain [9]. Improving micronutrient intake during pregnancy contributes to reduced micronutrient deficiencies in mothers and small increases in birthweight, and there is some evidence that infant survival after the first month may be improved. However, multiple micronutrient supplementation in pregnancy did not lead to a gain in perinatal survival in the pooled results of 11 studies of women receiving multiple micronutrient supplementation, and multiple micronutrients may increase the risk of birth asphyxia. Three-quarters of neonatal deaths happen in the first week of life, and the burden of mortality in the early neonatal period is much greater than

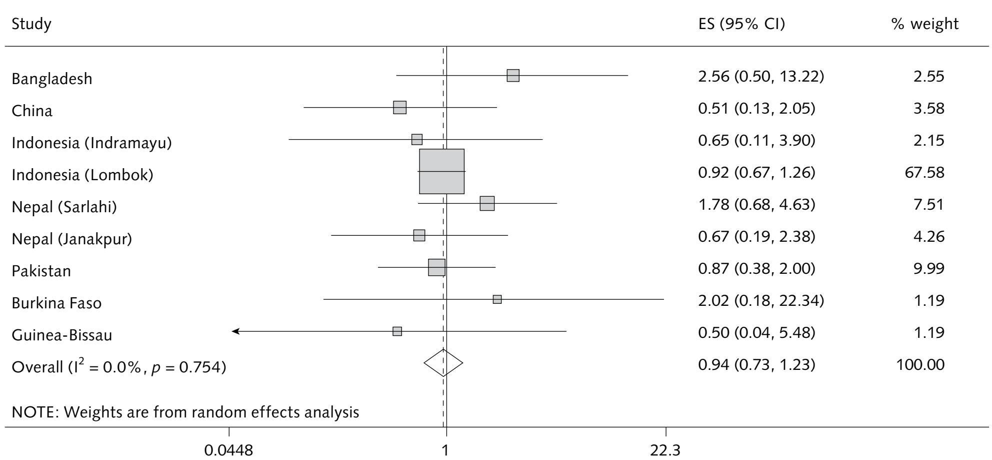

FIG. 7. Random effects model forest plots for effects of multiple micronutrient supplementation on late neonatal mortality. CI, confidence interval; ES, effect size

that in later infancy. There has also been little progress in reducing deaths during the perinatal period [31]. Given the limited resources available for public health in poor countries, attention should focus on interventions that are known to positively reduce the burden of stillbirths and early neonatal mortality. On current evidence, multiple micronutrient supplementation started in mid-pregnancy is not one of them. Success in reducing perinatal deaths is possible through outreach and community care, including health education to improve home care practices, to create demand for skilled care, and to improve care-seeking. Expansion of skilled care for babies and mothers is essential to achieve the reduction in neonatal deaths needed to meet the Millennium Development Goal for child survival.

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Multiple micronutrient supplementation during pregnancy in developing-country settings: Policy and program implications of the results of a meta-analysis

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Abstract

Background. *An independent Systematic Review Team performed a meta-analysis of 12 randomized, controlled trials comparing multiple micronutrients with daily iron–folic acid supplementation during pregnancy.*

Objective. *To provide an independent interpretation of the policy and program implications of the results of the meta-analysis.*

Methods. *A group of policy and program experts performed an independent review of the meta-analysis results, analyzing internal and external validity and drawing conclusions on the program implications.*

Results. *Although iron content was often lower in the multiple micronutrient supplement than in the iron–folic acid supplement, both supplements were equally effective in tackling anemia. Community-based supplementation ensured high adherence, but some mothers still remained anemic, indicating the need to concomitantly treat infections. The small, significant increase in mean birthweight among infants of mothers receiving multiple micronutrients compared with infants of mothers receiving iron-folic acid is of similar magnitude to that produced by food supplementation during pregnancy. Larger micronutrient doses seem to produce greater impact. Meaningful improvements have also been observed in height and cognitive development of the children by 2 years of age. There were no significant differences in the rates of stillbirth, early neonatal death, or neonatal death between the supplemented groups. The nonsignificant trend toward increased early neonatal mortality observed in the groups receiving multiple micronutrients may be related to differences across trials in the rate of adolescent pregnancies, continuing iron deficiency, and/or adequacy of postpartum health care and merits further investigation.*

Conclusions. *Replacing iron–folic acid supplements with multiple micronutrient supplements in the package of health and nutrition interventions delivered to mothers during pregnancy will improve the impact of supplementation on birthweight and on child growth and development.*

Key words: Antenatal care, birthweight, iron–folic acid supplementation, multiple micronutrient supplementation, neonatal death, pregnancy, stillbirth

Introduction

Anemia affects one-quarter of the world's population and is concentrated in preschool-aged children and women [1], and in the latter group it accounts for at least 20% of maternal mortality [2]. Because iron deficiency makes a large contribution to anemia, global efforts to reduce the anemia burden have largely been directed toward increasing intake of iron through supplementation, food fortification, and diversification of diet. Pregnant women are often deficient in several other nutrients, all of which can negatively affect them as well as their infants' health, growth, and development across the life course [3]. Although most developing countries have policies promoting iron–folic acid supplementation for women during pregnancy and lactation, few address other nutritional requirements women may have throughout this critical time.

Because multiple micronutrient deficiencies often

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coexist in developing-country settings, the use of multiple vitamin and mineral supplements has been proposed by some authors as an alternative to the current standard World Health Organization (WHO) recommendation for iron–folic acid supplements in pregnancy [4]. In 1999, a consultation of experts in the field, convened by UNICEF, WHO, and the United Nations University (UNU), agreed on a formulation for a multiple micronutrient supplement for pregnant women for trial purposes [5]. This supplement, which later became known as the United Nations International Multiple Micronutrient Preparation (UNIMMAP), contains 13 vitamins and minerals in addition to iron–folic acid (**table 1**).

Populations facing emergencies, including natural disasters and conflicts, often have limited access to food, and presently some relief food supplies are still not fortified with vitamins and minerals. Recognizing this potential problem and that micronutrient needs are greater during pregnancy and lactation, WHO/World Food Programme (WFP)/UNICEF published a joint statement recommending the provision of multiple micronutrient supplements to young children and to pregnant and lactating women in emergency situations to help prevent and control multiple micronutrient deficiencies [6].

An assessment of the impact on health outcomes of the use of multiple micronutrient supplements compared with an iron–folic acid supplement during pregnancy outside of emergency settings could be expected to help policy makers determine optimal approaches to improving maternal and infant heath, and to consider multiple micronutrient supplements during pregnancy when feasible and appropriate. This paper discusses the results of the meta-analysis involving 12 studies assessing the impact of the use of multiple micronutrient supplements on micronutrient status, birthweight and gestational age, fetal losses, and neonatal mortality that are reported in this volume. This paper explores the internal and external validity of the results and discusses the policy implications for making preliminary recommendations aiming at improving programs.

TABLE 1. Composition of the World Health Organization/UNICEF/United Nations University multiple micronutrient supplement (United Nations International Multiple Micronutrient Preparation [UNIMMAP])

Nutrient	Amount
Vitamin A	800 μg
Vitamin D	200 IU
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B^{1}	1.4 mg
Vitamin B^{2}	1.4 mg
Niacin	18 mg
Vitamin B^{6}	1.9 mg
Vitamin B^{12}	2.6 μg
Folic acid	400 μg
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 μg
Iodine	150 μg

Methods

The process that led to this meta-analysis is unusual and worthy of comment. This highly collaborative effort was performed by a diverse set of principal investigators, many of whom already had their own research funds, and who agreed to work together without a large amount of extra funding in order to increase the likelihood that their research would have policy and program impact. An initial meeting in 2002 of the principal investigators of nine efficacy and effectiveness trials of multiple micronutrient supplements from seven countries (Bangladesh, Guinea-Bissau, Indonesia, Nepal, Niger, Pakistan, and Tanzania) was held at the Institute of Child Health in London with funding support from the Micronutrient Initiative. The principal investigators, not all of whom were responsible for UNIMMAP trials, agreed to a standardized set of methods, including definition of outcome measures as well as consideration of a set of required and recommended confounders and effect modifiers that all should use [7]. A second meeting of the principal investigators of UNIMMAP trials (which included additional investigators from several other countries, including Burkina Faso and China, was held at the UNICEF Regional Office in Bangkok in 2004 to share preliminary results of the effectiveness trials that were already available [8] as well as to make initial explorations on how to do the meta-analysis of the efficacy trials. An independent Systematic Review Team was then commissioned by UNICEF/WHO/United Nations Standing Committee on Nutrition (SCN) to undertake a meta-analysis, and the principal investigators shared their data sets with them. A third meeting was held in October 2005 in Geneva under the aegis of the SCN, where the Systematic Review Team shared preliminary results of the meta-analysis with the principal investigators of 12 studies and began discussing the results obtained so far and further analysis to be undertaken. Tanzania and Vietnam were not included in the meta-analyses for operational reasons (such as lack of follow-up survey or lack of participation by investigators in meetings). It was agreed not to publish the results of the meta-analysis until each of the individual trials had been published. It was also agreed that all of the principal investigators would be part of the UNIMMAP study group team who would be the coauthors of the meta-analysis papers. A report of that meeting was prepared but not published because of the still confidential nature of the unpublished studies. Following completion of the meta-analysis, all of the principal investigators who were part of the UNIMMAP study group team agreed to the final versions of the four papers included in this volume [9–12].

It was also agreed at the principal investigators' meeting in Geneva that the policy and program members from the sponsoring agencies (SCN, UNICEF, and WHO) would review the results of these meta-analysis papers and independently make an analysis of the program and policy implications that stem from them. However, it is important to note that the funding agency (UNICEF) ensured that there was a strict firewall between the researchers at the University of Southampton who coordinated the meta-analysis and the sponsoring agencies [9] to ensure objectivity and their complete independence. Consideration of the policy and programmatic implications of the effect of micronutrient supplementation on birth outcomes requires several different perspectives, not least of which is to try to understand the possible mechanisms at play as well as what the biological significance of any such impact might be, and this is the purpose of this paper. Programmatic recommendations, as is well recognized, cannot always wait until there is perfect evidence for action, which may never come. The present writing group also took note that antenatal supplementation with multiple vitamins and minerals is the norm in many affluent countries and often for the affluent in poorer countries. In order to best interpret the results and to formulate conclusions and recommendations for policy and programs, this review looked at each of the outcomes and results that are reported in the meta-analysis papers. As well, the results in each of the individual trials were taken into account, along with a literature search using Medline and reference to existing normative program guidance.

Results

Trial population characteristics

As is to be expected of studies carried out on three different continents, the characteristics of the meta-analysis trial populations varied greatly. The review of methods and study characteristics by Margetts et al. [9] describes the large differences across the trials in baseline nutritional status. Mothers in Bangladesh [13], Indonesia [14, 15], Mexico [16], Nepal [17, 18], and Pakistan [19] were nearly 10 cm shorter than in those in Africa [20, 21] and China [22], whereas the mean body mass index (BMI) was highest in Guinea-Bissau [23], Mexico [16], and Zimbabwe [24]. Although the mean age did not differ across the trial populations, there were differences in parity, with 60% of mothers primiparous in China against only 19% in Pakistan. As Margetts et al. point out, the large differences in maternal size and parity across the trials need to be taken into consideration when interpreting the results of the meta-analysis [9].

Trial organization

There are important differences in the way the trials were organized that the review of trial characteristics does not capture entirely [9]. These organizational differences, summarized in **table 2**, relate to the way the trial effort and resources were employed. Some trials concentrated their efforts on delivering the supplements and carrying out the research, whereas others also tried to improve delivery of the supplements and improve compliance with supplement intake by the mothers, thus affecting the particular antenatal and postnatal health systems.

Most of the trials were carried out in predominantly rural populations, including Bangladesh, Burkina Faso, China, Indonesia (Indramayu and Lombok), Nepal (Sarlahi), Niger, and Vietnam. Only two of the trials, those in Guinea-Bissau (Bissau) and Zimbabwe (Harare), were carried out in urban settings. The remaining three trial populations, those in Mexico (Cuernavaca), Nepal (Janakpur), and Pakistan, were a rural–urban mix. Three trials, those in Guinea-Bissau, Nepal (Janakpur), and Zimbabwe, were "facility based," passively enrolling pregnant mothers coming to health centers. All other trials were "community based," actively seeking out mothers in the community early in pregnancy.

The way community surveillance was carried out also differed across the trials. In Bangladesh and Guinea-Bissau, the trials were conducted in the areas where existing health and demographic surveillance systems already had staff regularly recording vital events at the community level with follow-up household visits. In Burkina Faso, Mexico, and Nepal (Sarlahi), community-based surveillance was carried out by a trial workforce that had been employed for this purpose for the duration of the trial. In China, Indonesia, Niger, and Pakistan, the community surveillance was largely done by the existing community-based health workers as part of their regular job, although with varying levels of facilitation and extra training from the research project staff.

The trials also differed in the way resources were used to ensure adherence to the taking of the supplements, as well as to the collection of information and measurements. In the trials in Burkina Faso, Indonesia (Indramayu), Mexico, and Nepal (Sarlahi), a large part of the workers' efforts went into carrying out home visits to deliver supplements, take measurements, and record observations, with less or no effort going into improving the service delivery channels. In the

TABLE 2. Organizational aspects of the various trials of multiple micronutrient supplementation during pregnancy

Country of trial	Location Population size Rural or urban No. of births	Organizational focus/basis	Orientation of trial workforce	Stimulation of demand for services	Other components and comments
Bangladesh [13]	Matlab 225,000 Mostly rural 2,853	Community-focused DHSS and health facility for enrollment and examinations	DHSS workers check out all births and deaths in community Health service staff make household visits every 2 weeks to check adherence, take measurements, and collect data	Not reported	Food supplements made from local products provided through community-based organization as well as metronidazole to control bacterial vaginosis
Burkina Faso [21]	Hounde 12,000 Rural 1,260	Community-based surveillance and referral to health service for treatments, measurements, and delivery	Home visits monthly to check for pregnancies and household visits daily for supplement administration	None reported	Malaria treatment (2 types) and deworming 2× during pregnancy and vitamin A after delivery
China [22]	Shaanxi Population size not stated Rural 4,851	Community surveillance by village doctor and referral to township MCH facility as well as entry through health facility	Household visits every 2 weeks by village doctor to check adherence and by MCH staff after birth to take measurements and check vital events	Not reported	Not reported
Guinea-Bissau [23]	Bissau 90,000 Semiurban 2,100	Community for DHSS and health facility for enrolment and examinations	DHSS workers check out all births and deaths in community Health service staff make household visits to check compliance and to take measurements and collect information	Not reported	Malaria treatment and insecticide-treated bednets
Indonesia [14]	Indramayu 120,000 Rural 750	Community surveillance in research villages by research staff	Daily household visits for supplement administration. Weekly household visits for recording vital events and measurements	Not reported	Not reported

continued

TABLE 2. Organizational aspects of the various trials of multiple micronutrient supplementation during pregnancy *(continued)*

Country of trial	Location Population size Rural or urban No. of births	Organizational focus/basis	Orientation of trial workforce	Stimulation of demand for services	Other components and comments
Indonesia [15]	Lombok 2.1 million Mostly rural 28,426	Community-based facilitators linking to facility-based health workers (village midwives)	Household visits by both maternal data collectors and community-based facilitators to counsel	Social marketing and monthly household visits by community facilitators promoting health service utilization	Not reported
Mexico [16]	Cuernavaca Population size not stated Semirural 647	Community-based surveillance and research facility-based follow-up, plus referral as necessary to health service	Daily household visits for supplement administration	Not reported	High-quality antenatal care including referrals and treatment of infections. 1/3 of mothers were obese
Nepal [18]	Janakpur Population size not stated Rural and urban 1,052	Facility-based, with monthly clinic visits for examinations and measurements	Home visits monthly to check supplement administration and collect information	None reported	None reported
Nepal [17]	Sarlahi 650,000 Rural 4,130	Community-based surveillance and follow-up	Home visits monthly to check for pregnancies and household visits twice a week for supplement administration	Counseling on antenatal care and nutrition at the time of enrollment	Deworming and tetanus toxoid 2× during pregnancy Safe birthing kit for home-based delivery and flannel blanket for the newborn
Niger [20]	Maradi Population size not stated Mostly rural 2,550	Community workers (traditional birth attendants) actively seeking pregnant women and linking to nearest health facility	Traditional birth attendants dispensing supplements supported by community data collectors	Social marketing, plus outreach prenatal care from health facility to communities	Malaria chemoprophylaxis
Pakistan [19]	Sindh Population size not stated Rural and urban 1,613	Community health workers linking to facility (midwives) and community-based health workers (lady health workers), with referral as necessary to health system	Community health workers making household visits every 2 weeks to deliver supplements, make measurements, and collect information as appropriate	Social marketing and counseling at monthly household visit by community health workers	Not reported

Vietnam [25]	Red River Delta 515,000 Rural 1,579	Community surveillance by village health workers and referral to commune health facility	Research team collected routine health information from all 3 districts and did in-depth measurement and extra data collection through cluster surveys	Nutrition education for mothers during pregnancy through commune health facility	Not reported
Zimbabwe [24]	Harare Population size not stated Urban 1,106	Facility-based	Facility-based measurement, data and sample collection All supplements given at first contact and checked at birth	None	1/3 of mothers had untreated HIV infection

DHSS, Demographic Health Surveillance System; MCH, Maternal and Child Health

Indonesia (Lombok), Niger, Pakistan, and Vietnam trials, not only was the trial workforce used to help collect information and make measurements, but in addition extra efforts were put into trying to improve maternal adherence to the supplements by improving health service delivery mechanisms. Several trials even had social marketing and improved nutrition counseling that was aimed, not just at trial participants, but at the whole population of the communities in question.

In conclusion, the approaches used in organizing the trials varied considerably, ranging from a strictly research project approach to one of more in-depth program monitoring and evaluation. The strictly randomized control experimental approach provides greater scientific certainty that a treatment was delivered and that the only difference between the intervention group and the control group was the intervention being tested, assuming that measurements were done correctly. In the more programmatic approaches described above, delivery of the intervention relied more on getting the service delivery channel to function better, and then checking on compliance by a sample survey or some more indirect way. Community-based facilitation of service delivery can ensure early detection of pregnancy and increased uptake of health services, including micronutrient supplements. This energizing of the service delivery channel presumably improved all the antenatal and postnatal care. These organizational differences need to be taken into consideration when interpreting the results of the trials, and especially when trying to draw policy and program conclusions.

Adherence

Adherence was measured by pill counts or by observations of women actually consuming pills. The mean number of days women consumed the supplements was then reported as a percentage of the total number of possible days they could have consumed them (once they were recruited into the studies). If women consumed the supplements daily, adherence would be 100%. If women consumed them on average 5 days per week, adherence would be 71% (5/7 × 100). Adherence (often also referred to as compliance) was relatively high in all studies, with women consuming supplements on 69% to 98% of days (or, on average, 6 or 7 times per week (**fig. 1**).

The only true efficacy trials were the ones in Burkina Faso, Indramayu (Indonesia), and Mexico, where the research team administered the pills directly to the mothers in their homes on a daily basis. In Indramayu, Indonesia, two studies were conducted in parallel showing that the mean number of supplements consumed during pregnancy when women received them daily under direct observation was about 20% higher than the mean when they were distributed monthly

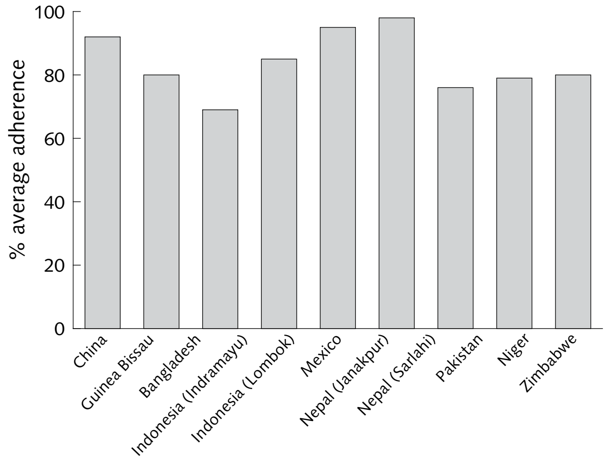

FIG. 1. Average adherence to supplementation in the meta-analysis studies

(130 vs. 107). The percentage adherence shown for Indramayu in **figure 1** is for the daily distribution group. In all other trials, the supplements were provided in batches in special bottles, and the number of pills not consumed was verified on replenishment. Early provision of supplements was made possible by the active "community-based" surveillance of pregnant women (in 8 of the 12 studies). Such early use of supplements meant that the numbers of supplements consumed in pregnancy in these studies were relatively high, ranging from 107 to 165, as compared with the WHO recommendation of 180 iron–folic acid supplements in pregnancy [26].

Micronutrient status

Maternal micronutrient status

The review by Allen and Peerson [10] reported that multiple micronutrient supplements had a similar impact on hemoglobin synthesis during pregnancy to that of iron–folic acid supplements alone, although often the multiple micronutrients contained lower amounts of iron. This may be because the women who received 60 mg of iron in an iron–folic acid supplement may not have absorbed it well, given the presence of inhibitors such as phytates and the likely low intakes of vitamin C, as is often the case among people in economically deprived settings with poor diets. The multiple micronutrient supplement, although containing only 30 mg of iron, also contained vitamin C, which may have helped absorption of the smaller amount of iron and so helped to ensure an equal effect in terms of the hematinic response.

Although micronutrient supplementation reduced anemia rates in all trials, significant levels of anemia still remained in most of them. In the Nepal (Sarlahi) study, 27.9% of women in the group receiving vitamin A and iron–folic acid and 37.7% in the group receiving multiple micronutrients were anemic in the third trimester, compared with 59.8% of those receiving only vitamin A. At 6 weeks postpartum, 15.2% and 12.2%, respectively, were anemic, although these levels were substantially lower than the level (39.8%) found in women who did not receive any iron in pregnancy [27]. Similar results were reported in Mexico, where about 30% of women in the group receiving multiple micronutrients and 32% of women in the iron–folic acid group had iron-deficiency anemia at 1 month postpartum [16]. In China, 45.1% of women who took iron–folic acid and 42.1% of those in the group receiving multiple micronutrients were anemic in the third trimester, compared with 61.0% of those who took folic acid alone [22].

One possible reason that anemia rates remained high among supplemented mothers in the meta-analysis trials is the lack of systematic control of infectious diseases. In Sarlahi, Nepal, intestinal parasites were presumptively treated twice during pregnancy, since previous studies had shown that women given albendazole in the second trimester of pregnancy had a lower rate of severe anemia during the third trimester [28]. The trials in Burkina Faso, Guinea-Bissau, and Niger included routine treatment of malaria. In Bangladesh, bacterial vaginosis was treated as one arm of the experiment, but the results of these interventions have not been reported yet. In Zimbabwe, a third of the mothers had HIV infections, although these were not treated.

Few trials assessed the impact of supplements beyond anemia, and they often did not look more broadly at maternal micronutrient status, especially for those nutrients contained in the multiple micronutrient supplements. In their accompanying review, Allen and Peerson [10] report inconsistent results for serum retinol status and suggest this may be due to poor absorption of the vitamin because of limited fat intake in the diet or to measurement problems. The Janakpur (Nepal) and the Indramayu (Indonesia) trials showed improvement in serum retinol in the mothers receiving multiple micronutrients compared with those receiving iron–folic acid, but this was not the case in the Pakistan trial. The Janakpur trial also showed improvement in serum vitamin E levels in mothers receiving multiple micronutrients that was not seen in the iron–folic acid group. Difficulties in assessment of zinc status may be the reason that the Indramayu trial showed no impact of the multiple micronutrient supplement on serum zinc levels and that the Pakistan trial is the only one that showed depressed serum zinc in the iron–folic acid group postpartum as compared with the group receiving multiple micronutrients, although similar results have been shown in multiple micronutrient supplementation of infants [29]. Several other studies have reported that concurrent deficiencies of nutrients other than iron are common in the trial sites, with the one in Mexico showing that zinc and folate deficiencies affected between 30% to 40% of women and that more than half had two concurrent deficiencies [16]. In Guinea-Bissau, 14% had low serum vitamin A values and 60% had poor serum folate status [30]. The Sarlahi study found that the rates of vitamin deficiency among control women in the third trimester were 66.9% for vitamin B_{12}, 88.4% for vitamin B_6, 63.6% for riboflavin, and 24.3% for vitamin D and that the levels of deficiency of these micronutrients were 35% to 77% lower among women who consumed multiple micronutrient supplements [31].

Impact on breastmilk and infant's micronutrient status

Very few trials in the meta-analysis reported the impact of maternal micronutrient supplementation on the micronutrient content of breastmilk or infants' micronutrient status. There is, however, considerable evidence from the literature that levels are improved by supplementation [32]. Maternal nutrient status during pregnancy affects the infant's nutritional status for many nutrients by improving infant stores and enhancing the micronutrient content of breastmilk [33, 34].

Size at birth

The meta-analyses observed a mean increase in birthweight of 22 g, with a range across studies from 4.9 to 75.5 g and with a larger impact on birthweight in infants of heavier women [11]. The effect of multiple micronutrient supplementation on birthweight was manifested by a positive shift in the entire birthweight distribution, with decreases in the numbers of low-birthweight (LBW) and small-for-gestational-age (SGA) babies and increases in the number of babies with weights at the other end of the curve. Fall et al. [11] report this increase as a higher rate of large-for-gestational-age (LGA) infants, which was defined as "birthweight above the within-each-population 90th percentile." Normally babies above 4 kg are considered LGA, and only in China, Guinea-Bissau, Lombok (Indonesia), and Zimbabwe were there several birthweights above 4 kg. There were no differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients in birth length or in head circumference of the newborns.

Birthweight differences can be a reflection of either shortened gestation, suboptimal fetal growth, or both, each with a different significance and prognosis [35]. The meta-analysis found no differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients in the rates of preterm birth or increased gestational length. Even though the meta-analysis noted some problems with measurement of gestational age in some of the studies, notably those in Niger and Pakistan, these results were no different if the improbable values were removed. This strongly suggests that the increase in birthweight of infants whose mothers received multiple micronutrients as compared with those whose mothers received iron–folic acid is a result of improved intrauterine growth, not decreased prematurity. The meta-analysis finding that the positive effect of multiple micronutrient supplementation on birthweight was greatest in infants of heavier women and was low or even negative among infants of women with low BMI is discussed later, but it is thought likely to be an artefact or to reflect that benefits accrue more to the mother and less to the fetus in women with low BMI than in women with higher BMI.

Further evidence from the individual UNIMMAP trials suggests that the impact of micronutrient supplementation during pregnancy on birthweight would be greater with larger doses of micronutrients. The study in Guinea-Bissau, which had two different multiple micronutrient supplements, one containing the RDA for nutrients and the other containing the same amount of iron but double the RDA for other nutrients, reported greater increases in birthweight with higher levels of micronutrients in the supplements (49 g for one multiple micronutrient vs. 88 g for two multiple micronutrients adjusted for malaria parasitemia, anemia, infant's sex, and season of birth [23]). Although the meta-analysis found no evidence that starting the supplement earlier in pregnancy increased the effect of the multiple micronutrient supplements on birthweight, the Niger trials found that the effect was greater when the duration of supplementation increased, so that the difference between infants in the multiple micronutrient group and those in the iron–folic acid group was 78 g for those whose mothers received the supplement for more than 150 days, compared with just 56 g for those whose mothers received the supplement for less than that period ($p < .001$) [20].

Several of the UNIMMAP intervention trials have now begun to report on growth and development outcomes later in childhood. In Nepal, children at the age of 2.5 years whose mothers had taken multiple micronutrients during pregnancy were heavier and although not taller, had larger head, chest, hip and mid-upper arm circumference, as well as lower systolic blood pressure of greater body size than those born to mothers who had only received iron–folic acid supplements [36]. A trial in Bangladesh reported small but significant improvements in measures of motor skills in children of mothers with low BMI who received multiple micronutrients during pregnancy [13]. The Vietnam trial in this volume reported that the increase in mean birthweight of approximately 100 g found in the districts of the Red River Delta supplemented with multiple micronutrients translated into a 30% reduction in stunting at 2 years of age [25].

Fetal and infant survival

The meta-analyses of mortality found no statistically significant differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients, be it for stillbirth rates in the 12 trials or for neonatal deaths in the 9 trials that reported on mortality after birth [12]. However, the early neonatal mortality rate was increased by 23%, although nonsignificantly, and when data from Lombok, Indonesia, were removed from the analyses because of significant heterogeneity ($p < .10$), there was a statistically significant higher odds ratio of early neonatal mortality in the groups receiving multiple micronutrients compared with the comparison groups (OR = 1.46; 95% CI, 1.09 to 1.95).

The lack of effect of the multiple micronutrient supplement on neonatal mortality, or even perhaps a negative effect in some locations, is surprising, considering the increase in birthweight achieved compared with the controls supplemented with iron–folic acid. Increased birthweight has consistently been found to be associated with a reduced risk of dying in infancy [37–39]. Even in Sarlahi (Nepal), an increase of 59 g in the mean birthweight of infants of women who were dewormed during pregnancy was associated with a 41% decrease in infant mortality at 6 months [28]. It seems strange that in the same Sarlahi population, similar increases in birthweight were reported to cause a decrease in mortality in one instance and an increase in another [40]. One possibility that has been suggested is that the multiple micronutrient supplements reduce early fetal losses but that infants then die later in the neonatal period [41].

Discussion

The success of these studies in attaining high rates of adherence to supplementation in both the multiple micronutrient and the iron–folic acid groups is noteworthy. Although daily iron supplementation is reported to cause more side effects than weekly supplementation [42], the findings of this meta-analysis confirm the findings of many other studies over the last two decades that women will consume iron, as well as multiple micronutrient supplements, as long as they have access to them and are adequately counseled on their use [43–45]. Furthermore, the meta-analysis found no significant differences in adherence between the multiple micronutrient and the iron–folic acid groups, even though the latter often received higher amounts of iron, and side effects were uncommonly reported. As commented by Margetts et al. [9], in 8 of the 12 studies, women were provided with supplements within the first 4 months of pregnancy. This early provision of supplements was made possible by the active community-based surveillance of pregnant women and is very different from the provision through facility-based approaches that is more commonly found in most Maternal and Child Health program settings. Such early use of supplements meant that the numbers of supplements consumed in pregnancy in these studies were relatively high, ranging from 107 to 165, as compared with the WHO recommendation of 180 iron–folic acid supplements in pregnancy [26].

The multiple micronutrient supplements were as effective as the iron–folic acid supplements in terms of the hemoglobin response, even though they often contained lower amounts of iron. In addition to vitamin C, which improves iron absorption, other nutrients in the multiple micronutrient supplements are likely to have contributed to improved hematopoiesis, such as retinol and selenium. These other nutrients are likely to have contributed to improving the nutritional status of the mother and, through her, the nutritional status of the infant, although these effects of the multiple micronutrients have so far been little researched. Another potentially important advantage of multiple micronutrients over the iron–folic acid supplements that is not apparent from the meta-analysis but that is beginning to raise concern, especially in the Indian subcontinent where many mothers are vegetarian, is the realization that giving iron–folic acid supplements without vitamin B_{12} can cause an imbalance in the metabolism of vitamin B_{12} and folate, which contributes to the metabolic programming of the offspring [46]. A study in Pune, India, has shown that children born to mothers with low vitamin B_{12} and high folate concentrations have higher insulin resistance [47]. Furthermore, a third of the mothers had low vitamin B_{12} status, and therefore giving them iron–folic acid supplements without vitamin B_{12} could well be contributing to the insulin resistance increasingly commonly seen in Indian children.

Why participants remained anemic in these trials, even though they were taking seemingly adequate amounts of supplemental iron, is not clear, but this has been seen in many effectiveness trials over the years. It may be that initiating supplementation in pregnancy is too late for many women, especially those with pre-existing anemia. A study conducted in Vietnam showed that the use of weekly iron–folic acid prior to and during pregnancy was associated with better iron status in the first and second trimesters of pregnancy and with reduced prevalence of LBW compared with pregnant women who only received daily iron–folic acid supplementation during pregnancy [48]. However, studies by Ekstrom et al. in Bangladesh comparing weekly and daily iron supplements found that a maximum hemoglobin effect was achieved by just 40 tablets each containing 60 mg of iron, whether taken as a daily or a weekly regimen, which led them to suggest that the level of iron supplementation currently being recommended might be too high [49]. However, anemia still persisted in these Bangladeshi women, even when the maximum hemoglobin response had been reached, with 20% still affected in the weekly and 14% in the daily regimes. This suggests that something else is involved in the causality of the anemia besides just iron availability.

One possible reason that supplemented mothers remain anemic could be infections, since these were not systematically treated across the trials. WHO/UNICEF program guidance for the control of anemia recommends the treatment of infections, and in particular of malaria, tuberculosis, HIV/AIDS, and helminth infections, in addition to the provision of iron supplements [50]. Inflammation associated with infections has been shown to contribute to low hemoglobin levels in iron-replete anemic pregnant women in Malawi [51] and Nepal [52], and the positive effects of multiple micronutrient supplements on hemoglobin levels in Kenyan adults with HIV/AIDS were only seen in subjects with no inflammation [53]. Furthermore, studies in schoolchildren in Kenya [54], South Africa [55], and Vietnam [56] all show that deworming, together with extra iron (either by supplementation or by fortification), resolves the problem of anemia better than either treatment alone.

Although none of the studies included in the meta-analysis have yet reported on the impact of maternal micronutrient supplementation on breastmilk composition or infant micronutrient status, there is considerable evidence from the literature indicating that these are improved. Maternal nutrient status during pregnancy affects the infant's nutritional status for many nutrients by improving infant stores and enhancing the micronutrient content of breastmilk [33, 35]. A study using antenatal multiple micronutrient supplements in Mexico found that vitamin A levels were improved in breastmilk [57] compared with the control group that received only iron. Studies in the Gambia have shown that riboflavin, vitamin A, and ascorbic acid concentrations in breastmilk can also be improved by micronutrient supplementation of lactating women [58–60]. In a double-blind study of low-income, lactating women in the United States, breastmilk levels of vitamin B_6, vitamin B_{12}, and folate increased in the micronutrient supplement group [61]. Zinc supplementation of Amazonian women during lactation doubled the retinol levels in breastmilk at 5 months postpartum compared with women receiving placebo [62]. Multiple micronutrient supplementation of HIV-positive mothers in Tanzania during pregnancy and lactation was associated with increased vitamin A and vitamin E status and decreased prevalence of vitamin B_{12} deficiency in infants at 6 weeks and 6 months postpartum [63]. Further research to demonstrate such linkages and benefits would be important to carry out. Many of the trials have collected samples that have yet to be analyzed and for which the results have not been published, and every effort should be made to ensure that this is done. Infants born with enhanced nutrient status are likely to be at an advantage for health and development.

It is remarkable that the increase in birthweight achieved by the multiple micronutrient supplement is of a similar order of magnitude to that produced by food supplementation during pregnancy. Kramer and Kakuma [64], in their Cochrane review of randomized, controlled trials of balanced energy–protein supplementation during pregnancy, reported a mean difference in increased birthweight of 37.6 g. Five of the nine trials that used UNIMMAP produced increases in mean birthweight greater than 30 g. The increase in mean birthweight achieved by use of the multiple micronutrient supplement is of course on top of any increase that might be achieved by the iron–folic acid supplements. Without a true placebo, we can only speculate on whether the iron–folic acid supplements also improved birthweight. However, there is a growing body of evidence which suggests that iron supplementation does improve birthweight, even in nonanemic women, suggesting benefits to maternal health beyond that seen for maternal anemia and iron deficiency, which may act through improving placental or fetal metabolism to facilitate fetal growth through pathways that do not involve maternal hemoglobin concentration [65].

Several newer trials, which were not included in the Cochrane review of multiple micronutrient supplementation [66] or in this meta-analysis that complements it, have also shown that multiple micronutrient supplementation during pregnancy increases birthweight. In a hospital-based trial among apparently healthy, well-nourished French women, a multiple micronutrient supplement without iron taken during the last 6 months of pregnancy not only improved blood levels of vitamin B_2, vitamin B_6, vitamin C, vitamin E, β-carotene, and folate, but also increased birthweight by 251 g as compared with the placebo [67]. The results of a hospital-based trial among thin (BMI < 18.5) and/or anemic women in New Delhi, India, showed that a supplement containing 29 vitamins and minerals taken in addition to the regular iron–folic acid supplement during the last trimester of pregnancy increased birthweight by 98 g, increased birth length by 0.80 cm, and reduced early neonatal morbidity by 50% [68], as compared with placebo. The increase in mean birthweight meant that the incidence of LBW was reduced from 43.1% to 16.2%, which seems truly remarkable in the Indian context, where a third of all births are LBW. If the results of this New Delhi trial can be replicated in other locations, multiple micronutrient supplementation could provide an important new tool for trying to solve the LBW problem in India.

The meta-analysis finding that the positive effect of multiple micronutrient supplementation on birthweight was greatest in heavier women and was low or even negative among women with low BMI is not easy to interpret. It may in part be an artefact caused by the way mothers' BMI status was determined, whereby weight on entry was regressed linearly to 15 weeks. Since weight gain in pregnancy is not linear, this will overclassify as thin those who entered the study early. Although admitting that the trials were not designed to examine interactions with maternal size, Fall et al. [11] hypothesized that the thinner mothers were not able to utilize the micronutrients because they were energy deficient. This seems unlikely, however, since among undernourished mothers (assessed by mid-upper-arm circumference < 23.5 cm) in the Lombok (Indonesia) trial, the multiple micronutrient supplement had a stronger positive effect on birthweight than the iron–folic acid supplement [15], a result similar to that seen in the trial of multiple micronutrients among thin women in New Delhi [68]. Furthermore, a similar partitioning was shown in mothers receiving food supplements, with the benefits accruing more to the mothers and less to the fetus in mothers with low BMI as compared with mothers with higher BMI [69]. This suggests that the partitioning of effect observed in women with low BMI who receive micronutrient supplements either is an artefact produced by the method of analysis or is due to something other than, or in addition to, energy sufficiency.

A low BMI in a mother can also be a reflection of younger age and greater immaturity. In the United States, where menarche occurs at around 12 years of age and girls continue to grow until 18 years of age on average, late-maturing girls tend to be thinner and grow taller than early-maturing girls [70, 71]. In developing-country settings, many girls, especially those in rural areas, are still growing into their late teens and even past 20 years of age [72]. Research in the United States has shown that if a still-growing adolescent becomes pregnant, her growth hormones favor the partitioning of growth to the mother at the expense of the fetus [73]. In energy-rich environments such as the United States, this results in the still-growing adolescent's accumulating extra fat at the end of the pregnancy. In energy-poor environments of rural Bangladesh, however, pregnancy and lactation during adolescence result in weight loss and depletion of fat and lean body mass, as well the cessation of linear growth of the mother [74]. A study in Mexico also found that multiple micronutrient supplements increase energy intake by the mother during pregnancy [75], which in an energy-rich environment is likely to contribute to increased fat accretion.

These partitioning and energy-saving mechanisms, which operate under hormonal control during first pregnancies among still-growing adolescents, could be attenuated more by the multiple micronutrient supplements than by the iron–folic acid control supplements. Zinc supplementation has been shown to increase growth and the production of insulin-like growth factors in Vietnamese children [76]. It may be that the zinc in the multiple micronutrients stimulates the production of growth hormone factors, which promote the growth of the young, still-growing child–mother at the expense of the growth of her fetus.

For most biological outcomes, the optimal birthweight is greater than the mean birthweight, and although the highest risk of an undesirable outcome is usually found for birthweights below 2.5 kg, the lowest risk is usually in the 3.5- to 4-kg group [77]. The outcomes that follow this pattern are many and include infant mortality in populations with high levels of intrauterine growth retardation (IUGR) [78] and cognitive function in the United Kingdom [79], for example. Thus, when a small increase in mean birthweight occurs and is evenly distributed across the whole population, as is the case for the increase in birthweight associated with the use of multiple micronutrient supplements, the whole population benefits. In the meta-analyses, very few if any infants had birthweights above 4 kg except for those in China, Guinea-Bissau, Lombok (Indonesia), and Zimbabwe.

Optimal fetal and infant growth is increasingly recognized to confer many benefits across the life course. As shown in the Vietnam trial reported in this volume, the small increase in mean birthweight achieved by multiple micronutrients as compared with iron–folic acid resulted in a 30% reduction in stunting rates in these children at 2 years of age [25]. These findings are similar to those achieved by food supplements provided during the last 3 months of pregnancy to mothers in Java, Indonesia, whereby a birthweight increase of nearly 100 g resulted in a 20% reduction in stunting at 5 years of age [80]. Reducing the rate of LBW is recognized to confer substantial economic benefits [81], and improved fetal and infant growth is recognized to contribute greatly to improving human capital across the life course [82], including reduction in the risk of diabetes and high blood pressure later in life [83].

It is of great concern that although the meta-analysis of mortality found no statistically significant differences in the rates of stillbirth or neonatal death between the groups of mothers supplemented with multiple micronutrients and those supplemented with iron–folic acid, the risk of early neonatal mortality was increased by 23% [12]. Although not statistically significant, this effect was seen in all trials except the two in Indonesia. Although the meta-analysis found no significant difference in the effect on the rate of premature births between mothers supplemented with multiple micronutrients and those supplemented with iron–folic acid, evidence from the trials in China [22] and Sarlahi (Nepal) [17] suggests that both multiple micronutrient and iron–folic acid supplements reduced the rate of premature births as compared with a control. However, the multiple micronutrient supplements not only reduced the rate of premature births but also reduced the rate of IUGR and shifted the whole birthweight distribution upward [84]. It may be that larger babies are the source of the possible excess neonatal mortality, causing problems for young adolescent primiparous mothers with relatively narrow, immature birth canals in particular. The rate of premature births also appears to be higher in this group of mothers, so conversely, excess neonatal mortality may be due to increased mortality among nonviable premature neonates born to young adolescent primiparous mothers.

But perhaps what is most surprising is that the apparently negative effect of the multiple micronutrient supplement is in the neonatal part of the reproductive losses. If multiple micronutrients were causing harm to the fetus, one would expect it to manifest itself more in stillbirths, but this did not occur. However, not only is there no evidence of harm to the fetus, but to the contrary, there seems to be benefit, as reflected in lower stillbirth rates and greater birthweight. Any possible negative impact seems to be in the neonatal part of the reproductive losses, which is more likely to be a reflection of the condition of the mother and placenta, the standard of health care during delivery and postpartum, or both.

The meta-analysis of mortality outcomes did not look at the possible interactions of the effects of micronutrient supplementation with maternal BMI and/or parity, as was done in the meta-analysis of birth size. However, several of the individual trials reported that the lack of effect, or even the negative effects, of the multiple micronutrient supplement compared with the iron–folic acid supplement occurred mainly in primiparous mothers. In Lombok (Indonesia) the beneficial effects of multiple micronutrient supplements on 90-day mortality found overall was not seen in primiparous mothers or young mothers (< 19 years of age). In Burkina Faso, the negative effect of multiple micronutrient supplements was associated with primiparity, although the effect was not statistically significant ($p = .11$) [21].

Some insights into the possible causes of the lack of impact, or even the possible negative impact, of the multiple micronutrient supplements on neonatal mortality are afforded by looking at the results obtained by trials that used other "controls" and different types of multiple micronutrient supplements. The Sarlahi (Nepal) trial [85] found no significant difference in 90-day mortality between the group receiving vitamin A plus iron–folic acid and the group receiving multiple micronutrients as compared with the local "control" mothers receiving only vitamin A supplements. But although both vitamin A plus iron–folic acid and multiple micronutrient supplements significantly reduced mortality among preterm infants as compared with controls, and both increased birthweight, the multiple micronutrient supplement, but not the iron–folic acid supplement, increased birthweight across the whole distribution [84]. Interactions between these differences in neonatal mortality and maternal parity, age, or BMI were not reported, but other studies at the Sarlahi trial site have found that in primiparae, young maternal age (< 18 years) is associated with an increased risk of preterm delivery as compared with a maternal age of 19 to 25 years [86]. The offspring of younger mothers also have a higher neonatal mortality rate [87]. The possibility that the decreased rate of preterm deaths and the increased rate of term deaths in the group receiving multiple micronutrients in Sarlahi were concentrated in still-growing adolescent mothers whose birth canals had not yet fully developed seems a likely one.

Prematurity was also part of the picture in the China trial [22], where the groups receiving multiple micronutrient and iron–folic acid supplements were compared with the "control" mothers receiving supplements of folic acid. Although there were no differences in the mean duration of gestation between the group receiving iron–folic acid and the group receiving multiple micronutrients, there were significant increases in duration of gestation in both groups compared with the folic acid control group. Furthermore, even though birthweight increased only in the group receiving multiple micronutrients, early neonatal mortality was significantly reduced only in the iron–folic acid group as compared with the folic acid control group. Although there were more first pregnancies in the Chinese than in the Sarlahi mothers (63% vs. 26%), the Chinese mothers were on average 2 years older and 8 cm taller, and only 1% of the Chinese mothers were under 18 years of age. Zeng et al. [22] further suggested that the difference in early neonatal mortality in the China trial was caused by the different levels of iron in the supplement (60 mg in the iron–folic acid supplement and 30 mg in the multiple micronutrient supplement), and that the differences in neonatal mortality seen in all the other trials except Lombok (Indonesia) were also caused by this difference between supplements in iron level.

Unlike all the other trials, the risk of early neonatal mortality was greater in the iron–folic acid group in both the Lombok and the Indramayu trials in Indonesia. This was the case even though in the Indramayu trial, the multiple micronutrient supplement contained 30 mg of iron and the iron–folic acid supplement contained 60 mg of iron, as opposed to the Lombok trial, in which both supplements contained 30 mg of iron. Furthermore, the beneficial effects of the multiple micronutrient supplement on early infant mortality in the Lombok trial were improved when the supplement was provided by the local village midwife and the birth attendant was a trained one. A large nationwide study in Indonesia has shown that the provision of postnatal care has a strong protective effect on neonatal mortality, with a progressive reduction in the risk of neonatal death as the percentage of deliveries by trained birth attendants increases [88]. It seems likely that the difference in the effect of the multiple micronutrient supplement on early neonatal mortality in Indonesia as compared with elsewhere is a reflection of the greater adequacy of perinatal health care provided by its extensive network of village midwives.

Care is needed before drawing rapid and inappropriate conclusions from the meta-analysis of mortality. The Lombok (Indonesia) trial was removed from the meta-analysis of mortality primarily because of its contribution to the between-study heterogeneity for the early neonatal mortality outcome. But it was not removed for the other outcomes, such as birthweight. The heterogeneity of the effect of multiple micronutrient supplements on early neonatal mortality may well be more a reflection of the adequacy of perinatal health care than of differences in the biological causes of early neonatal mortality and/or of the conditions of the mother rather than those of the fetus. Furthermore, in Lombok, mortality in the second and third months of life was 25% lower among infants of mothers who had received multiple micronutrients than among infants of mothers who had received iron–folic acid [15]. It is worth remembering also that the relationship between birthweight and infant mortality is population specific, and consequently the same birthweight interval does not have the same mortality risk in different ethnic or racial groups [89].

The meta-analysis raises the question as to whether the increase in birthweight caused by the multiple micronutrient supplement is potentially dangerous and might be contributing to increased neonatal mortality, as suggested by the investigators in the Sarlahi trial [84]. However, as the meta-analysis of birth size pointed out, the part of the body most likely to increase the risk of cephalopelvic disproportion is the head, and head circumference was not increased by the multiple micronutrient supplements. One study that has looked at the effect of food supplementation on birthing difficulties in detail is a trial in the Gambia where food supplements fed to mothers during pregnancy produced an increase in mean birthweight of 126 g, which was not associated with increased birth complications, and the increase in head circumference was only of the order of 1 mm [90]. Although the UNIMMAP trials were not powered to test the effect on maternal mortality, there was no evidence that the multiple micronutrient supplements increased maternal deaths in the large Lombok (Indonesia) trial, for example, and the Guinea-Bissau trial reported "substantial reductions in maternal mortality" in the group receiving multiple micronutrients [23], although the authors did not present the data and the trial was obviously not powered to look at this outcome.

The proportion of women with BMI less than 18.5 was relatively low in Africa (5.5% in Guinea-Bissau and 11% in Burkina Faso) and in the Asia-Pacific region (8.3% in Indonesia and 10.7% in China) but was higher in South Asia (20.4% in Pakistan, 27.9% in Janakpur, and 28.5% in Bangladesh). This may be a reflection of teenage pregnancy rates, which are well known to be high in the Indian subcontinent. For example, the proportion of women who have begun childbearing by age 17 is 20% in Nepal [91] and 37% in Bangladesh [92], which indicates the need for more attention to this issue from a children's rights perspective. Although 21% of women in Burkina Faso have also begun childbearing by age 17, they are taller than women in the Indian subcontinent when they begin childbearing [93]. The percentage of women aged 15 to 19 with height below 145 cm is less than 1% in Burkina Faso compared with 14.2% in Nepal and 15.7% in Bangladesh. It is essential that programs in South Asia address the nutritional status of women throughout the life course in order to reduce the prevalence of low BMI, low height, and associated health issues during pregnancy, for the sake of both the mother and the child. In these contexts, food-based supplements should be the product of choice, but in addition to rather than instead of multiple micronutrients (or through a fortified-food supplement, such as a lipid-based nutrient supplement or a ready-to-use supplementary food). In other populations, screening women for low BMI and low height and providing such women with increased food intake along with multiple micronutrients would be appropriate. These actions should go hand-in-hand with improving delivery and neonatal care, along with ongoing efforts to improve health and education systems, health and nutrition services capacity, and water and sanitation interventions.

Clearly there is a need for a single, consolidated source of WHO policy and program guidance on maternal nutrition during pregnancy and lactation, expanding on the program guidance on mothers' health and nutrition that is contained in the Global Strategy on Infant and Young Child Feeding [94]. Given the existing recommendation on the use of multiple micronutrients in emergencies, urgent attention needs to be paid to why the use of multiple micronutrients has not been expanded, when many women are experiencing the same negative factors while in a supposedly non-emergency situation.

Although there is a WHO recommendation that blanket supplementation with balanced protein–energy foods should be provided to women during pregnancy where LBW rates are greater than 15% [95], this is not widely appreciated, and neither is there program guidance on how to do it. The WHO Reproductive Health Strategy [96] mentions the word nutrition only twice and anemia not at all. Further discussions and review of existing program guidance are also contained in the SCN Policy Paper No. 18 on Low Birthweight [97], but little or none of this program guidance covers issues related to adolescent nutrition and teenage pregnancy. Although the need for a continuum of health and nutrition care across antenatal and early childhood periods in order to promote optimal fetal and infant growth and development is increasingly recognized, the translation of this into comprehensive programmatic guidelines for delivering the appropriate packages of interventions is still lacking and is urgently needed.

The lack of program guidance is perhaps a reflection of the complexity of the relationships between maternal nutrition and reproductive health outcomes and the failure of the nutrition community to adequately describe them to date. There is an urgent need to develop and strengthen the monitoring and evaluation of programs aimed at promoting improved maternal, fetal, infant, and young child nutrition, growth and development [98].

What are the implications of our findings for public health? Given the apparent benefits of multiple micronutrient supplementation, any suggestion of possible harm must be carefully reviewed to consider alternative explanations and to balance the potential gains and harms. Improving micronutrient intake during pregnancy reduces micronutrient deficiencies in mothers and increases birthweight. The surprising finding in the meta-analyses of a higher rate of early neonatal mortality in the group receiving multiple micronutrient supplementation when Lombok (Indonesia) was excluded underscores the need to enhance maternal and neonatal health care services in developing countries to improve the nutritional status of women prior to pregnancy and to protect maternal and neonatal health care during delivery. This conclusion is strongly reinforced by other aspects of maternal health and mortality and the inadequate progress towards Millennium Development Goal 6. The fact that women with low BMI are disadvantaged in many ways also reinforces the recommendations of the final report of the WHO Commission on Social Determinants of Health, which suggests, among other actions, increased focus on adolescent girls and on the circumstances of childbirth, as well as on child development, education, and social protection [99]. Increased attention must be given to improved community care to address households and pregnant women while current efforts to strengthen health systems go ahead. Whatever is recommended, and however cautiously the findings of the meta-analysis are interpreted, program and policy makers, donors, or indeed researchers, should not be let off the hook with regard to the need to make public health changes, given the urgent need to do something about the unnecessary deaths and poor development of millions of mothers and children in poor environments; somehow the intergenerational cycle of growth failure needs to be broken.

Conclusions

In summary, improving micronutrient intake during pregnancy reduces micronutrient deficiencies in mothers and increases birthweight. This paper suggests that multiple micronutrients are just as effective as iron–folic acid in reducing anemia and that good adherence can be achieved with maternal micronutrient supplements during pregnancy when the supply is guaranteed and mothers are counselled positively, including counselling on normal side effects. When so provided, multiple micronutrients increase mean birthweight and reduce the incidence of LBW, which also leads to improved child growth and development. The findings point to the need for improving maternal nutritional status before as well as during pregnancy, since intervening in pregnancy is too late. In settings where there is a significant number of undernourished pregnant women, supplementary feeding is also needed. The findings point to the importance of an integrated approach to addressing infectious disease (worms, malaria) along with nutritional status during pregnancy in order to bring about the necessary improvement in birthweight. The finding again reinforces the message that we cannot address Millennium Development Goal 4 without addressing Millennium Development Goal 5. Furthermore, there is an urgent need to take on the issue of adolescent pregnancy from a both from a children's rights and children's protection perspective, as well as from a gender perspective. This is perhaps one of the most urgent and critical of gender issues to be resolved in Millennium Development Goal 3, and that also has implications for the achievement of many of the other Millennium Development Goals.

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